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**Behavior Modification for Cognitive Health in Aging:  
A Justifiable Public Health Agenda?**

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**M.A.  
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**An abstract of  
A thesis submitted to the Faculty of the  
Rollins School of Public Health of Emory University  
in partial fulfillment of the requirements for the degree of  
Master of Public Health  
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2012**

**Abstract**  
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Rising life expectancies and reductions in chronic disease mortality have resulted in an increasing prevalence of cognitive impairment in the United States, with high societal and personal costs, widespread fear, and a thriving marketplace of cognitive solutions that have not received official sanction. Cognitive health in aging has therefore emerged as an urgent public health issue. However, the intersection of gerontology, cognition, and public health has received little academic attention to date. This qualitative research project examines the question, *Why have no public health recommendations been issued nationally for older Americans to maintain or promote their cognitive health?* and the deeper epistemological questions, *What is adequate evidence for issuing public health recommendations?* and *When do we know enough to act?* Using a grounded theory framework, it examines spoken discourse of seven cognitive health researchers. The project first evaluates epidemiological and randomized controlled trial (RCT) evidence associating cognitive engagement, vascular factors, physical activity, and social engagement with cognitive health outcomes. It then examines arguments made for or against issuing public health recommendations, using the Toulmin model of analyzing arguments. The analysis revealed four epistemological arguments for or against recommending public health recommendations for cognitive health: 1) the *Evidence-Based Policy Argument*, which uses RCTs alone to warrant issuing recommendations, 2) the *Epidemiologically Informed Policy Argument*, which proposes that epidemiology and RCTs together constitute adequate evidence, 3) the *Triangulated Evidence Policy Argument*, built around a cumulative weight of multiple forms of evidence to support recommendations, and 4) the *Logically Derived Policy Argument*, which uses RCT evidence that supports behavioral risk factor prevention to endorse the same behavior to prevent a common cognitive sequela of the disease risk factor. This project ultimately endorses the *Logically Derived Policy Argument* in support of heart-healthy behaviors for cognitive health.

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## Chapter 1

### Introduction

*...we have an aging population that lives too long, in which their brains don't live as long as their bodies.<sup>1</sup>*

Michael Merzenich, Ph.D.,  
Posit Science CEO and neuroscientist

The prevalence of cognitive impairment is growing in the United States as the population steadily ages, making cognitive health an increasingly important public health priority. Improved living conditions helped in the control of infectious diseases and facilitated the epidemiological transition, a shift in the balance of prevalence from infectious and acute diseases to chronic conditions.<sup>2</sup> Infant and child mortality rates plummeted in western developed countries, and the average life expectancy in the U.S. rose from 48 years in 1900 to almost 79 years today.<sup>3</sup> As populations have aged they have accumulated a greater prevalence of neurodegenerative diseases such as those linked to dementia.<sup>4</sup> Moreover, the brain ages as does the rest of the body.<sup>5</sup> A conservatively estimated 36% of Americans age 71 and older, or 8.8 million people, have some degree of cognitive impairment, according to functional assessments, and 14%, or 3.4 million, have full-blown dementia.<sup>6</sup> As more people live to higher ages and

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<sup>1</sup> Michael Merzenich, interview by author, San Francisco, CA, October 3, 2011.

<sup>2</sup> Abdel R. Omran, "The Epidemiologic Transition: A Theory of the Epidemiology of Population Change," *Milbank Quarterly* 49, no. 4 (1971): 509-538.

<sup>3</sup> The exact life expectancy reported was 78.9. Sherry L. Murphy, Jiaquan Xu, Kenneth D. Kochanek, "Deaths: Preliminary Data for 2010," *National Vital Statistics Report* 60, no. 4 (2012): 1-51.

<sup>4</sup> Kiyotaro Kondo, "Rising Prevalence of Neurodegenerative Diseases Worldwide," *Internal Medicine* 35, no. 4 (1996): 238.

<sup>5</sup> Timothy A. Salthouse, "Selective Review of Cognitive Aging," *Journal of the International Neuropsychological Society* 16, no. 5 (2010): 754-60.

<sup>6</sup> The actual prevalence figures were 31.1% for cognitive impairment and 13.9% for dementia only, in 2002. The data is from the Aging, Demographics, and Memory Study. These estimates use both cognitive measures (the Mini-Mental State Exam) and functional measures

comprise a larger portion of the population, the prevalence of cognitive impairment is expected to expand further; using the rate of 36%, about 18 million Americans age 70 and up will be cognitively impaired by 2030.<sup>7</sup>

The effects of dementia are not confined to patients. A 2001 estimate put the cost of informal (non-institutionalized) care alone at \$18 billion annually.<sup>8</sup> It is three times as costly for Medicare to care for someone with dementia than for someone of the same age without dementia.<sup>9</sup> Caregivers often experience worsening health conditions, reporting fatigue, pain, depression, stress, and weight gain.<sup>10</sup> In addition, although its prevalence is not as high as other chronic conditions such as cardiovascular disease, dementia seems to evoke a disproportionate amount of fear among the general population. A PARADE/Research! America poll of one thousand Americans over the age of 17 found that 62% feared losing their mental capacity compared with 29% who

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(the Dementia Severity Rating Scale and the Clinical Dementia Rating) to estimate cognitive impairment among both communities and long-term care facilities. B.L. Plassman et al., "Prevalence of Dementia in the United States: The Aging, Demographics, and Memory Study," *Neuroepidemiology* 29, no. 1-2 (2007): 125-32.; Brenda L. Plassman et al., "Prevalence of Cognitive Impairment without Dementia in the United States," *Annals of Internal Medicine* 148, no. 6 (2008): 427-434.

<sup>7</sup> Numbers obtained from "Table 2. Projections of the Population by Age, Sex, Race, and Hispanic Origin for the United States," 80. Jennifer Cheeseman Day, *Population Projections of the United States by Age, Sex, Race, and Hispanic Origin: 1995 to 2050*, U.S. Bureau of the Census Current Population Reports P25-1130 (Washington, DC: U.S. Government Printing Office, 1996), <http://www.census.gov/prod/1/pop/p25-1130.pdf> (accessed October 31, 2012).

<sup>8</sup> Kenneth M. Langa et al., "National Estimates of the Quantity and Cost of Informal Caregiving for the Elderly with Dementia," *Journal of General Internal Medicine* 16, no. 11 (2001): 770-8.

<sup>9</sup> Julie P. W. Bynum et al., "The Relationship between a Dementia Diagnosis, Chronic Illness, Medicare Expenditures, and Hospital Use," *Journal of the American Geriatric Society* 52 (2004): 187-194.

<sup>10</sup> National Alliance for Caregiving and Evercare. *Evercare Study of Caregivers in Decline: A Close-Up Look at the Health Risks of Caring for a Loved One: Report of Findings September 2006*, National Alliance for Caregiving, [www.caregiving.org/data/Caregivers%20in%20Decline%20Study-FINAL-lowres.pdf](http://www.caregiving.org/data/Caregivers%20in%20Decline%20Study-FINAL-lowres.pdf) (accessed September 11, 2012).



feared losing their physical capacity.<sup>11</sup> A MetLife Foundation poll of 1000 Americans over the age of 41 found that 20% of respondents specifically feared Alzheimer's disease more than cancer, heart disease, stroke, or diabetes.<sup>12</sup>

Fear is insidious. A survey of people aged 40-60 and found that 35.5% of them looked for dementia in themselves in one or more ways, such as repeatedly checking for symptoms of dementia, assuming that perceived cognitive changes are dementia, or asking for confirmation of perceived symptoms from others. This type of symptom seeking has been called "anticipatory dementia."<sup>13</sup> It has even been argued that Americans have a particular fear of dementia because of the value that we place on autonomy, so that "senility haunts the landscape of the self-made man."<sup>14</sup> Cognitive impairment is a major risk factor for institutionalization,<sup>15</sup> which in turn can entail loss of independence, financial difficulty, and social isolation.

Considering the psychosocial context, there appears to be an urgent need for advice on what to do to maintain cognitive health. The media seem happy to oblige in this respect. In addition, there is a thriving marketplace for cognitive health products and services includes brain health supplements, stress reduction techniques, and brain wellness coaching. One of the most visible cognitive health businesses is the brain fitness software industry, which grew 35% in one year,

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<sup>11</sup> See Lynda A. Anderson et al., "The Public's Perceptions about Cognitive Health and Alzheimer's Disease among the U.S. Population: A National Review," *The Gerontologist* 49, no. S1 (2009):S3-S11.

<sup>12</sup> Ibid.

<sup>13</sup> See Stephan J. Cutler and Lynne Gershenson Hodgson, "Anticipatory Dementia: A Link between Memory Appraisal and Concerns about Developing Alzheimer's Disease," *The Gerontologist* 36, no. 5 (1996):657-664.

<sup>14</sup> Jesse Ballenger, *Self, Senility, and Alzheimer's Disease in Modern America: A History* (Baltimore: Johns Hopkins University Press, 2006), 153.

<sup>15</sup> Melanie Luppá et al., "Prediction of Institutionalization in the Elderly," *Age and Ageing* 39, no.1 (2010): 31-38.

from 2008 to 2009, to reach \$295 million in revenues in 2009.<sup>16</sup> The marketing for these products appears to speak to aging populations who are concerned about their cognitive health.

Cognitive health in aging has emerged on the national policy stage. In 2005 Congress had established the Healthy Brain Initiative (HBI) within the Healthy Aging Program (HAP) at the Centers for Disease Control and Prevention (CDC) in partnership with the Alzheimer's Association to "address cognitive health with a focus on lifestyle issues."<sup>17</sup> The Healthy Brain Initiative appeared to represent something new by articulating a health perspective, referencing the positive outcome of maintaining cognitive health. In its central document published in 2007 for the public health world, the HBI argues broadly that "Given the tremendous burdens described, their impact, and the developing science, public health should step forward to address cognitive health" and articulates a "lofty but achievable longterm goal: *To maintain or improve the cognitive performance of all adults.*"<sup>18</sup> It emphasized emerging science supporting vascular risk factors and physical inactivity as lifestyle factors that can be modified to promote cognitive health.

In April 2010 the National Institutes of Health held a State-of-the-Science Conference on Preventing Alzheimer's Disease and Cognitive Decline, examining the evidence for behavior change for cognitive health at the population level.

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<sup>16</sup> According to SharpBrains annual market research report, the brain fitness software industry alone grew million in revenues. See *Transforming Brain Health with Digital Tools to Assess, Enhance and Treat Cognition across the Lifespan: The State of the Brain Fitness Market* (San Francisco: SharpBrains, 2010).

<sup>17</sup> Centers for Disease Control and Prevention and the Alzheimer's Association, *The Healthy Brain Initiative: A National Public Health Road Map to Maintaining Cognitive Health* (Chicago, IL: Alzheimer's Association, 2007), 8.

<sup>18</sup> *Ibid.*, 1-2.

Although the State-of-the-Science Conference was framed around cognitive decline and Alzheimer's disease, one of the six research questions that it evaluated evidence for was "*What are the therapeutic and adverse effects of interventions to improve or maintain cognitive ability or function?*," a question closely related to public health promotion for cognitive health. At the Conference's closing, an independent panel of health professionals and public representatives issued a statement that "firm conclusions cannot be drawn about the association of *any modifiable risk factor* with cognitive decline or Alzheimer's disease."<sup>19</sup> Regarding the question about interventions to improve or maintain cognitive health, it stated that "Despite some encouraging associations found in observational studies, RCTs [i.e., randomized controlled trials] of specific interventions have not *definitively* established positive therapeutic effects on maintaining or improving cognitive function, or preventing cognitive decline."<sup>20</sup>

The State-of-the-Science Conference Statement challenged programs devoted to promoting cognitive health in older adults by suggesting that they had no scientific foundation to move ahead with any messaging. Following the release of the Statement, HAP Director Lynda Anderson noted that "to pursue this whole thing of lifestyle interventions when our federal colleagues would be opposed to it doesn't make sense." After the conference, the HBI emphasized other efforts, such as surveillance of the public health burden of cognitive impairment, a process that usually precedes and justifies a community-based

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<sup>19</sup> Martha L. Daviglus et al., "National Institutes of Health State-of-the-Science Conference Statement: Preventing Alzheimer's Disease and Cognitive Decline," *NIH Consensus and State-of-the-Science Statements* 27, no. 4 (April 2010). Emphasis mine.

<sup>20</sup> *Ibid.*

health focus.<sup>21</sup> However, the State-of-the-Science Conference Statement had drawn emotional responses during the meeting and later in the media and in the public commons, as well as among some cognitive aging experts who expressed disappointment and frustration at the reading of the evidence. Negative reactions to the conference from researchers included that it was “very negative,” “very unhelpful,” and that “they’re behind the field here....There was a lot of disenchantment with the NIH report.”<sup>22</sup> Other experts stood by the statement as a judicious message about the state of the science to date, as “very accurate.”<sup>23</sup>

In fact, an unbridgeable gulf appears to lie between a constant stream of published advice on what to do to keep one’s brain healthy, on the one hand,<sup>24</sup> and the State-of-the-Science Statement that nothing has been proven to maintain or improve cognitive function, on the other. The urgency remains unanswered and the stream of media advice goes unabated. This qualitative research project addresses the question, *Why have no public health recommendations been issued nationally for older Americans to maintain or promote their cognitive health?* Within the context of the demographic imperative (almost 20% of Americans will be over the age of 65 by the year 2030), expected rising prevalence of dementia, and pervasive fear of dementia, the answer is only partially provided by the State-of-the-Science Conference Statement. The wider issue really is, *What is adequate evidence for issuing public health*

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<sup>21</sup> Lynda Anderson, interview by author, Atlanta, GA, November 21, 2011.

<sup>22</sup> Peter Rabins, interview by author, Baltimore, MD, August 11, 2011; Peter Whitehouse, interview by author, telephone, September 19, 2011; George Rebok, interview by author, Baltimore, MD, August 11, 2011, respectively.

<sup>23</sup> Jennifer Manley, interview by author, New York, NY, October 11, 2011.

<sup>24</sup> Anna E. Vandenberg et al., “How Do Top Cable News Websites Portray Cognition as an Aging Issue?” *The Gerontologist* 52, No. 3 (2011): 367–382.

*recommendations?* or *When do we know enough to act?* Several possible answers to these epistemological questions emerge from the documents and interview transcripts analyzed for this project.

The first viewpoint, expressed in the State-of-the-Science Conference Statement, is that of evidence-based medicine and evidence-based practice. The approach endorses the randomized controlled trial (RCT) as the level of evidence needed to establish truth. Only by randomly and blindly assigning interventions against a control group who do not engage in the intervention can those interventions be tested for efficacy. An assumption behind this viewpoint is that only the detailed “truth” can be disseminated to the public. I call this the *Evidence-Based Policy Argument*.

The second viewpoint is that less rigorous observational evidence will suffice in certain circumstances for establishing behavioral recommendations. Although generally regarded as less conclusive than RCTs, observational studies include prospective longitudinal designs with representative samples that attempt to causally link exposures or behaviors earlier in life with health outcomes later in life. Another approach is to study homogeneous populations (such as an order of nuns) in order to control for and thereby rule out confounding factors such as socioeconomic status or diets.<sup>25</sup> According to the second argument type, an abundance of such associations may constitute enough proof for issuing public health messages, especially when a situation is time sensitive, RCTs are prohibitively expensive, and interventions (such as

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<sup>25</sup> A good example of this is the so-called Nun Study by epidemiologist David Snowdon. See the lay tradebook: David Snowdon, *Aging with Grace: What the Nun Study Teaches Us about Living Longer, Healthier, and More Meaningful Lives* (New York: Bantam Books, 2001).

preventing someone from exercising) would be unethical. The advice given does not necessarily have to be at a detailed, prescriptive level. I call this *Epidemiologically Informed Policy Argument*.

A third viewpoint is a combination of the preceding two. In this case, it is the combination and cumulative weight of evidence that can be used to recommend behavior change. In addition to RCTs and epidemiological evidence, one might add quasi-experimental data, formative research, and narrative. I call this the *Triangulated Evidence Policy Argument*.

A last viewpoint is a different way of combining the first and second arguments. In this case, RCTs showing that a particular lifestyle behavior is effective in preventing a risk factor for a certain disease can be used to argue that the same behavior can prevent a common cognitive sequela of that disease. For example, evidence linking heart disease risk with cognitive impairment suggests that behaviors that reduce the incidence of heart disease will reduce the incidence of cognitive impairment. According to this viewpoint, evidence combined with logic make a strong enough case to provide recommendations, although research may need to be continued to establish the parameters of these recommendations. With this approach, the Multiple Risk Factors Intervention Trial that provided strong evidence for a low cholesterol diet, no smoking, and exercise to reduce risk of cardiovascular disease<sup>26</sup> might support the recommendation to exercise to reduce the risk of dementia in a population. Those who use this perspective often

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<sup>26</sup> Jeremiah Stamler and James D. Neaton, "The Multiple Risk Factor Intervention Trial (MRFIT)—Importance Then and Now," *JAMA* 300, no. 11(2008): 1343-5.

refer to “common sense” (putting two and two together) in the absence of RCTs. I call this viewpoint the *Logically Derived Policy Argument*.

My project examines the evidence for lifestyle behavior change for cognitive health from the perspective of a public health gerontologist. In addition to the research data itself, my evidence is the collection of arguments made for or against issuing public health recommendations based on extant evidence. Occasionally, as with the ACTIVE Trial, the Impact Trial, and the evidence for the vascular-cognitive connection, where it is a strong focal point of the discussion, I examine the evidence directly in order to illustrate the various interpretations of that evidence. But the focus of the investigation is on the filters, or arguments, through which the evidence is presented.

## Chapter 2

### Literature Review

This project examines a disciplinary intersection within public health gerontology that has received little attention to date. Table 2.1 illustrates how unusual the topic of healthy cognitive aging has been within gerontology. There were 252 articles with the term “cognition” and 890 articles with the term “cognitive” in the title or abstract of three prominent gerontology journals, *The Gerontologist* and *The Journals of Gerontology: Series A and B*, between 1961 and October 2012. This number constitutes about 13.6% of the approximately 8370 articles published. However, even within gerontology the issue of cognitive or brain *health* has barely been covered at all, with coverage starting as recently as 2001. Cognitive research tends to be framed in terms of disease or decline.

In contrast, there were 12 article abstracts that included the word “cognition” and 88 articles with the word “cognitive” in the abstract between 1911 and October 2012 in the *American Journal of Public Health*, constituting only .3% of the approximately 33,150 articles published. These searches suggest that while cognition is an important issue within the field of gerontology, it goes virtually unmentioned within the field of public health, although public health does cover aging issues. Meanwhile the term “public health” was mentioned in only 86 gerontology abstracts, or only about 1% of the time.

Two recent influential papers from prominent psychologists illustrate the debate over whether to issue public health recommendations related to cognitive health. The divergent conclusions drawn by these scholars are based on different types of evidence and on different justifications for how this evidence supports



**Table 2.1. Occurrences of cognitive terminology in titles and/or abstracts of leading gerontology and public health journals\***

<b>Search term</b>	<b><i>The Gerontologist and The Journals of Gerontology: Series A and B from 1961 (abstract or title field)</i></b>	<b><i>The American Journal of Public Health from 1911 (abstract field)</i></b>
Cognition	252 (1973)	12 (1993)
Cognitive	890 (1970)	88 (1975)
Cognitive function or cognitive functioning or functioning cognitively	261 (1987)	18 (1977)
Cognitive performance or perform cognitively	76 (1991)	4 (1977)
Age-related cognitive change	5 (1999)	0
Cognitive improvement, improve cognition, or improving cognition	2 (2003)	0
Maintain cognition, maintaining cognition, maintain cognitive, maintaining cognitive, or cognitive maintenance	4 (2009)	0
Healthy cognition or healthy cognitive	3 (2008)	0
Brain health or healthy brain	9 (2001)	0
Cognitive health or healthy cognition	17 (2009)	2 (2008)
Dementia	643 (1980)	16 (1983)
Alzheimer's or Alzheimer disease	355 (1981)	7 (1987)
Cognitive impairment or cognitively impaired	247 (1983)	21 (1989)
Cognitive decline or declining cognition	101 (1989)	2 (2008)
Mental health	253 (1961)	318 (1975)
Public health	86 (1995)	n.a.
Age or aged or aging	n.a.	2584 (1921)

\*Notes: Search was conducted on October 22, 2012; Dates following article count indicate the first mention of the term in the title and/or abstract.

the conclusions. The same can be said for the researchers interviewed in this project, helping us arrive at what is at stake in these differing conclusions for public policy. Ultimately it seems that reading the evidence in an interdisciplinary fashion is required to endorse public health recommendations for cognitive health. As the opening debate and subsequent interviews show, remaining within strict disciplinary boundaries cannot move public health forward or meet its moral imperative to alleviate suffering.

In 2006, Dr. Timothy Salthouse of the University of Virginia took on the issue of the benefits of mental activity in an article titled “Mental Exercise and Mental Aging: Evaluating the Validity of the ‘Use It or Lose It’ Hypothesis.”<sup>27</sup> Salthouse is a towering figure in the field of cognitive psychology, having documented “robust” cognitive performance declines in aging and having proposed the processing speed theory of cognitive aging as a common cause explanation.<sup>28</sup> His article depicts the *use it or lose it hypothesis*, the idea that mental activity can preserve mental functioning in aging, as a generally accepted folk theory that has little empirical support.<sup>29</sup> The popularity of the theory, he says, is supported by “a plethora of anecdotal observations, what seems to be a compelling analogy to the effects of physical exercise on physical functioning, and

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<sup>27</sup> *Perspectives on Psychological Science* 1, no. 1 (2006): 68-87.

<sup>28</sup> See, for example, Arthur F. Kramer et al., “Environmental Influences on Cognitive and Brain Plasticity during Aging,” *The Journals of Gerontology* 59A, no. 9 (2004): 940-941.

<sup>29</sup> Timothy A. Salthouse, “Mental Exercise and Mental Aging: Evaluating the Validity of the ‘Use It or Lose It’ Hypothesis,” *Perspectives on Psychological Science* 1, no. 1 (2006): 68-87. In this article Salthouse attributed the first reference of the concept in the field of cognitive aging to Josephine Curtis Foster & Grace A. Taylor in 1920. See “The Applicability of Mental Tests to Persons over 50,” *Journal of Applied Psychology* 4, No. 1 (March 1920): 39-58.

a commitment to the assumption that humans can exert control over their own destiny by choice of lifestyle.”<sup>30</sup>

Salthouse reviews evidence for the claim that “the rate of mental aging is moderated by amount of mental activity,” including training interventions, rates of aging of experts in particular domains (e.g., chess) and occupational groups (e.g., professors) and leisure activities (e.g., crossword puzzles) and found that the trajectories of growth and decline in cognitive abilities represent the same curvilinear shape. After usefully pointing to many methodological problems in this field of study, Salthouse summarizes the evidence to argue against the *use it or lose it hypothesis* because the variables of activity and aging do not interact to change the shape of decline. In other words, all people have worse performance in old age no matter how much time they have spent acquiring skills or experience. However, Salthouse seems to favor an overly constrained interpretation of the *use it or lose it hypothesis* by claiming that behavior must change rate of aging. He himself admits at the end of his article that enhancing skill or ability earlier in life may have the net effect of delaying the manifestation of decline later in life. Although he does not use the term, this possibility is a restatement of Fries *compression of morbidity hypothesis* and a central tenet of health promotion in aging. This theory suggests that against an assumed finite life span and trends towards fewer disabilities and better health, illnesses can be compressed into a shorter and shorter period of time before death. Where health can be extended long enough, death will arrive before illness and marked decline,

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<sup>30</sup> Salthouse, “Mental Exercise and Mental Aging: Evaluating the Validity of the ‘Use It or Lose It’ Hypothesis,” 84.

drastically reducing both personal suffering and societal expense. Fries asserts his idea as both a theory and a preventive health manifesto to be pursued by policymakers.<sup>31</sup> The point is, who really cares about the academic finding that the rate of aging occurs universally and is the same across people, if the real effect is that cognitively engaged people have more years of cognitive functioning because they have built up higher skill level?<sup>32</sup> If the latter is true we need to encourage mental activity through public health action.

Hertzog, Kramer, Wilson, and Lindenberger (2004)<sup>33</sup> respond directly to Salthouse, but they broaden their focus from mental exercise and the *use it or lose it hypothesis* to what they call the *cognitive-enrichment hypothesis*, which looks at all behaviors that can potentially affect cognitive functioning in old age including cognitive, social, and physical engagement.<sup>34</sup> Their broadened claim is that “a variety of factors, including engaging in intellectually and mentally stimulating activities, both (a) slow rates of cognitive aging and (b) enhance

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<sup>31</sup> James Fries, “Aging, Natural Death, and the Compression of Morbidity,” *New England Journal of Medicine* 303, no. 3 (1980):130–35.

<sup>32</sup> Interestingly, Salthouse is eloquent in advising cognitive engagement anyway, concluding his article with the statement that “Although my professional opinion is that at the present time the mental-exercise hypothesis is more of an optimistic hope than an empirical reality, my personal recommendation is that people should behave as though it were true. That is, people should continue to engage in mentally stimulating activities because even if there is not yet evidence that it has beneficial effects in slowing the rate of age-related decline in cognitive functioning, there is no evidence that it has any harmful effects, the activities are often enjoyable and thus may contribute to a higher quality of life, and engagement in cognitively demanding activities serves as an existence proof – if you can still do it, then you know that you have not yet lost it,” *ibid.*, 84-85.

<sup>33</sup> Christopher Hertzog, Arthur F. Kramer, Robert S. Wilson, and Ulman Lindenberger, “Enrichment Effects on Adult Cognitive Development: Can the Functional Capacity of Older Adults be Preserved and Enhanced?” *Psychological Science in the Public Interest* 9, no. 1 (2009):1-65.

<sup>34</sup> *Ibid.*, 3: “Thus, rather than speaking of cognitive use or cognitive exercise, we generically refer to all behaviors that potentially enhance cognition as forms of cognitive enrichment. The cognitive-enrichment hypothesis states that the behaviors of an individual (including cognitive activity, social engagement, exercise, and other behaviors) have a meaningful positive impact on the level of effective cognitive functioning in old age. We subsume the use-it-or-lose-it hypothesis under this more general cognitive-enrichment umbrella.”

levels of cognitive functioning in later life.” Claim (b) shifts the argument into dialogue with public health concerns and the desire to promote the compression of morbidity rather than rate of aging *per se*. The argument alludes to the Baltes and Baltes model of successful aging<sup>35</sup> by discussing ranges of developmental abilities throughout life, both plasticity and restricted potential with age, selectivity of activity throughout the life course that affects abilities, and the ability for knowledge (pragmatics) to compensate for process declines (mechanics) in age.

Hertzog et al. state that one of the main reasons their conclusions differ from those of Salthouse is that they include longitudinal studies whereas he does not, and “[t]o ignore this longitudinal evidence is to discount some of the strongest evidence for cognitive-enrichment effects.”<sup>36</sup> It must be noted that by including longitudinal evidence these researchers are reaching across traditional disciplinary lines to include epidemiological data that has traditionally been the purview of public health rather than cognitive psychology. This interdisciplinary approach, they demonstrate, changes one’s conclusions. They examine longitudinal data associating mental activity, physical activity, and social activity in adulthood with later onset of cognitive dysfunction, skill training with transfer effects on attention and other areas of executive functioning that are particularly vulnerable to cognitive aging, and aerobic training effects on executive functioning, to name a few. The authors call evidence accumulated since 2000

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<sup>35</sup> Paul B. Baltes and Margret M. Baltes, “Psychological Perspectives on Successful Aging: The Model of Selective Optimization with Compensation,” in ed. Paul B. Baltes and Margret M. Baltes, *Successful Aging: Perspectives from the Behavioral Sciences* (Cambridge: Cambridge University Press, 1990), 1-34.

<sup>36</sup> Hertzog et al., “Enrichment Effects on Adult Cognitive Development,” 41.

that aerobic exercise enhances cognitive function in older adults “overwhelming.” Notice, again, that the emphasis is placed on enhancement rather than on slowing cognitive aging. This perspective dovetails with the neuropsychological concept of building cognitive reserve for longer cognitive functioning.<sup>37</sup>

I will examine some of the evidence for cognitive effects later in this chapter but for now let us look at how Hertzog et al. connect the evidence to their claim. They do it as follows:

Given the problems associated with assessment of change over long time intervals (years or even decades, in the case of the cognitive-enrichment hypothesis), developmental researchers must consider evidence from multiple, different observational and intervention designs. The sources of evidence range from cross-sectional associations, longitudinal panel studies, experimental intervention in human and animal populations, and neuroimaging studies to computational models. The characteristics of each of these different approaches – their strengths and weaknesses regarding the enrichment process – need to be taken into account as one is attempting to identify the mechanisms and estimate the possible amount of cognitive-enrichment effects in human cognition.<sup>38</sup>

The passage above endorses the interdisciplinary method of triangulation.<sup>39</sup>

Through triangulation, researchers acknowledge that each type of evidence has its own weakness. By pooling data together in examination of the same research question, researchers using this approach attempt to come up with a more complete answer than if they looked at one data stream alone. This is a very different perspective than the sequential process endorsed by the *Evidence-*

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<sup>37</sup> See, for example, Yaakov Stern, “What Is Cognitive Reserve? Theory and Research Application of the Reserve Concept,” *Journal of the International Neuropsychological Society* 8 (2002): 448-460.

<sup>38</sup> *Ibid.*, 10-11.

<sup>39</sup> See Norman Denzin’s description of this social science research method, “Strategies of Multiple Triangulation,” in *The Research Act* (Chicago: Aldine Publishing Company, 1970): 297-313.

*Based Policy Argument*, where observational studies lead to clinical trials, which lead to policy. After backing this interdisciplinary warrant, the researchers allude to a public health crisis, with “staggering health care costs in the United States.” In addition, they suggest that public opinion has left public policy behind because “our society is proceeding forward as if the case [i.e., that cognitive enrichment benefits cognitive functioning] is closed, and public policy will need to understand that reality and attend to it.”<sup>40</sup> By this they mean that companies marketing cognitive products with health claims are economically thriving. They draw parallels with health campaigns that have changed behavior for societal benefit: “Public campaigns have raised public awareness about the risks of tobacco consumption and have influenced its use, and similar efforts may lead to better fitness, more active engagement in life, and so on, with derivative benefits,”<sup>41</sup> further developing their moral backing for change.

In my reading, the article endorses public health messaging for cognitive health. Although behavior may not necessarily change the rate of aging, it can have other public benefits and for this reason recommendations for these behaviors could be issued. The authors write, “Our point has been that enrichment effects can have positive benefits even when they do not address the underlying cause of incipient cognitive decline. For instance, physical activity can delay the onset of cognitive loss associated with dementia and normal aging.”<sup>42</sup> Such delay, representing a compression of morbidity, could translate to enormous public health savings in terms of prevented institutionalization. The

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<sup>40</sup> Hertzog et al., “Enrichment Effects on Adult Cognitive Development,” 48.

<sup>41</sup> *Ibid.*, 48-49.

<sup>42</sup> *Ibid.*

authors note that pointing out the connection between longer community residence and an active lifestyle could even be used to motivate the public to engage in these healthful behaviors.<sup>43</sup> Lastly, the authors point out that behaviors cannot guarantee outcomes because the evidence only guides us “on a probabilistic basis,”<sup>44</sup> a comment that seems to sum up the limitations of all evidence in relation to any public health, or even clinical issue.

The debate between Salthouse and Hertzog et al. illustrates how cognition can be framed differently in relation to public health. Whereas Salthouse stayed within the disciplinary purview of cognitive psychology and took a focused view of a tight hypothesis, in my view Herzog et al. used a moral imperative to broaden the issue in public health terms, raising the stakes and also raising questions about the types of evidence that should be called on to answer the question, *What public health recommendations can be made to promote cognitive health in aging?* I begin the discussion of arguments for public health recommendations by describing the trials that constitute the main support for evidence-based practice built around cognitive engagement.

### **The ACTIVE and IMPACT Trials**

Cognitive engagement has a dubious place among lifestyle interventions for cognitive health. A large public health review of evidence on brain aging and the prevention of dementia did not even bring up the subject.<sup>45</sup> Cognitive engagement encompasses leisure activities that are considered to be cognitively

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<sup>43</sup> Ibid., 47.

<sup>44</sup> Ibid., 49.

<sup>45</sup> Mary N. Haan and Robert Wallace, “Can Dementia Be Prevented? Brain Aging in a Population-Based Context,” *Annual Review of Public Health* 25 (2004):1-24.



demanding as well as cognitive training exercises, which are usually targeted practice exercises in cognitive tasks to develop particular abilities. Interventions range from pairing elders with children in elementary schools for mutual cognitive stimulation as in the well-known Baltimore-based Experience Corps to computer-based cognitive fitness training. The most cited intervention with applicability to public health is the Advanced Cognitive Training for Independent and Vital Elderly study, or the ACTIVE Trial. Because it is the largest and most comprehensive of RCTs to date, with claims to impressive benefits lasting at least five years, examining the evidence found in ACTIVE is a useful focus for our cognitive engagement discussion.

### ACTIVE

Funded by the National Institute on Aging and the National Institute of Nursing Research from the year 2000, ACTIVE enrolled 2,802 community-dwelling adults aged 65 and up who had no significant impairments. Participants were randomly assigned to one of three cognitive training interventions or a control group. They received either memory training (mnemonic strategies for remembering verbal material), reasoning training (strategies for identifying serial patterns in letter or word lists), speed of information processing (computerized visual search under divided attention conditions), or nothing (controls). Participants were not blinded to their conditions although assessors were. The interventions were carried out in ten 60-75-minute group sessions over a 5-6 week period. The study looked at two sets of outcomes. First, it measured cognitive or “proximal” outcomes, which were neuropsychological tests in the areas of intervention: verbal memory tests, a pen and pencil pattern

identification task, and a computer-administered visual identification test. Second, the study examined a set of four “primary outcomes” that were functional in nature and had been correlated with the trained abilities as well as with recognized public health goals such as keeping elders out of institutions. First, participants report their self-rated difficulty on a standard set of instrumental activities of daily living (IADLs) from the Minimum Data Set – Home Care that are known to be cognitively demanding, such as managing finances or using medication. The study authors call this outcome “IADL Difficulty” and they refer to it as an index of dependency because those who performed badly on many such activities often need to be placed under someone else’s care. They were also rated on two performance measures. First, participants were evaluated on “Everyday problem solving,” which required them to identify information in printed materials and perform behaviors with the information, such as making change. Second, participants were evaluated on “Everyday Speed of Processing,” which required them to perform activities such as looking up phone numbers or to perform reaction time tasks. In an attempt to investigate an effective “dose” of the intervention, the researchers further randomized a subset of participants of the training sessions to receive “booster” training at 11 and 35 months after initial training with four 75-minute sessions.

The first study report that occurred two years after baseline testing revealed that cognitive training had significant proximal effects under all three intervention conditions: memory training had boosted memory performance, reasoning training reasoning performance, and speed of processing training processing speed. These gains are consistent with much other research observing

cognitive training effects. These gains remained for the first two years of follow-up, but decreased with time. None of the conditions, however, had any effect on the primary functional outcomes. Cognitive training, therefore, did not “transfer” to real-world tasks. The investigators did not expect transfer for a variety of reasons and had prepared to do a long-term study. One reason was that many participants were performing well initially and had no room to improve over a short period of time. Another was that they were not old enough to have experienced age-related cognitive decline, a factor that was clear by lack of cognitive decline in the control group which could be compared to the potential stability or gains in the intervention groups.<sup>46</sup>

Three years later, a landmark article on the study was published reporting on results five years after baseline testing. Of the original participants, 67% were still with the study and due to attrition of the worse off represented a comparatively healthier group. Five years out, the immediate improvements in proximal abilities were still higher than controls, suggesting durable cognitive training effects. Those who received the speed-of-processing booster and the reasoning booster held onto their improvements in their respective abilities five years out better than those who had not received the booster. The effect size for the speed of processing intervention on speed of processing performance was 0.76 (0.62 to 0.90), versus effect sizes of 0.23 (0.11 to 0.35) and 0.26 (0.17 to 0.35) for memory training and reasoning training, respectively, on their corresponding performances. The effect of the speed of processing intervention

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<sup>46</sup> Karlene Ball et al., for the ACTIVE Study Group, "Effects of Cognitive Training Interventions with Older Adults: A Randomized Controlled Trial," *JAMA* 288, no. 18 (2002): 2271-81.

was even greater with booster training, at 0.85 (0.61 to 1.09). The authors define this effect size in terms of training improvement from pre-training to year 5 minus the control's improvement during the same period, divided by intra-subject standard deviation on adjusted composite scores.<sup>47</sup> On the more important functional measures (i.e., how the cognitive training transferred to everyday living), the reasoning training group (serial pattern training) had a significant effect of 0.29 (0.03 to 0.55) on self-reported IADL Difficulty, encompassing tasks such as preparing food and were observed to perform them better than they would have had they not received the intervention. The study also found reported decline in IADLs for the other two intervention groups that did not reach significance but had similar effect sizes. After controlling for baseline age and cognitive function, participants in the speed of processing group that had received booster training were 30% better at performance on everyday speed of processing than those who hadn't received booster training.<sup>48</sup> It is important to note that these "improvements" seem to be decreases in declines, suggesting better maintenance of health versus any improvement.

The ACTIVE Trial could be a useful model for public health intervention because it is built around sample means rather than individual scores. In addition, it specifically addresses the potential population aging issue of expected age-related cognitive decline (age-graded norms) and ways to cancel out those declines with gains.<sup>49</sup> The authors admit that their finding that cognitive training

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<sup>47</sup> Sherry L. Willis et al., "Long-Term Effects of Cognitive Training on Everyday Functional Outcomes in Older Adults," *JAMA* 296, no. 23 (2006): 2811.

<sup>48</sup> *Ibid.*, 2812.

<sup>49</sup> Ball et al., "Effects of Cognitive Training Interventions with Older Adults," 2278.

had an effect on daily functioning is “limited,”<sup>50</sup> although they do expect greater results with further follow up. There were also a number of other limitations. Recruitment could have led to a self-selecting group of better performing elders and therefore not be representative of most American elders. In addition, analysis of attrition throughout the study showed that those remaining in the study tended to be better performers across all experimental groups. This is a problem common to many studies, as it is a challenge to attract a diverse group of participants and also sustain their participation. The difficulty here may be because cognitive function testing is perceived as more personally invasive or more burdensome than physical function testing. This study was single-blind, so that the participants knew the condition to which they were assigned, although the researchers did not. Participants may have been influenced by their attitudes and beliefs about the condition to which they were assigned. Finally, the lead author of the original study and a participant in the second study, Dr. Karlene Ball of the Center for Research on Applied Gerontology at the University of Alabama Birmingham, owned an interest in Visual Awareness Inc., the company that makes the Useful Field of View, the speed-of-processing assessment tool used. This potential conflict of interest raises the possibility of additional bias in the study.

The ACTIVE Study presents weak evidence that cognitive training improves cognitive functioning. The finding that reasoning training transferred to reported activities of daily living needs to be verified by functional assessments

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<sup>50</sup> Willis et al., “Long-Term Effects of Cognitive Training on Everyday Functional Outcomes in Older Adults,” 2812. The study is ongoing.

beyond self-reports under unblinded conditions. If the other interventions, speed of processing and memory, were close to reaching significance on decline of IADLs as the authors indicate, that needs to be shown in the same way with larger samples. These results need to be duplicated for it to be convincingly claimed that cognitive training can reduce the types of functional declines that tend to lead to poor quality of life, need for care, and even institutionalization. As the study continues, it would be helpful if functional IADL assessments could be added to the self-reports and those compared with age-graded norms.

### IMPACT

ACTIVE was followed by the IMPACT Trial, which used the Useful Field of Review instrument that had boosted speed of visual processing in the ACTIVE Trial.<sup>51</sup> Funded by the cognitive fitness software producer Posit Science Corporation, IMPACT was a three-site study involving 487 people age 65 and up. Recruitment and selection were similar to the ACTIVE Trial (recruitment through advertisements and presentations and selected if they were age 65 and up without significant impairments). Participants were randomized into either an experimental group that used Posit Science's Brain Fitness Program or an active control that received a computer-based program of factual information from disciplines such as history, art, and literature. The training programs lasted an hour each day, five days a week, for eight weeks (a total of 40 hours) and were therefore much more intensive than in the ACTIVE Trial. Unlike the ACTIVE Trial, participants as well as administrators were blinded to the conditions. The

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<sup>51</sup> Glenn E. Smith et al., "A Cognitive Training Program Based on Principles of Brain Plasticity: Results from the Improvement in Memory with Plasticity-based Adaptive Cognitive Training (IMPACT) Study," *Journal of the American Geriatric Society* 57, no. 4 (2009):594-603.

study's primary measure was an index score from six subtests for orally presented speech concerning memory and attention from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Because Brain Fitness trains auditory processing speed and RBANS measures memory and attention performance, the researchers effectively assert that a measurable improvement in RBANS would constitute a transfer effect. In order to add more sensitivity to the findings and to pinpoint the source of any generalizability found in the RBANS score, investigators included seven secondary measures, a "directly trained measure of exercise performance derived from the experimental training processing speed exercise" (no details provided) as well as six neuropsychological measures that used orally presented speech (the Rey Auditory Verbal Learning Test (RAVLT), Rivermead Behavioral Memory Test (RBMT), and Wechsler Memory Scale (WMS-III)). In addition, they administered a pre-post assessment on the Cognitive Self-Report Questionnaire CSRQ-25. Unlike in the ACTIVE Trial, evaluation took place at an unspecified time soon after recruitment, without a one-year, two-year, or five-year followup so there is no measure of the durability of effect.<sup>52</sup>

The study found that mean performance on RBANS increased 3.9 points on average for the experimental training group, a significant 2.1 points higher than for the active control. Both groups started out very close to the ceiling of 100 points (96 points on average for the experimental training group and 96.6 for the active control), so the gain may be impressive. The authors had mentioned

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<sup>52</sup> Ibid. It is due to this lack of followup that the IMPACT Study was not included in the State-of-the-Science review.

this ceiling as an explanation for why they recruited other secondary measures of memory and attention.

The study reported significantly larger mean improvements on all secondary measures except the Rivermead Behavioral Memory Test for the experimental testing group over the active controls: an average 60 millisecond greater drop in mean processing speed by the experimental training group which trained on that measure over the active control group, a 3.2-point better score in overall memory, a 2.2 better score on the total RAVLT a .6-point better score on the RAVLT word list delayed recall, a .5-point better score on the WES-III digit span backwards test, a .4-point better score on the WES-III letter-number sequencing test, and a .025 better score on the CSRQ-25 test.<sup>53</sup>

The experimental trial participants had an average drop in processing time of 68 milliseconds from a mean of 116 milliseconds (with huge standard deviation) to a mean of 48 milliseconds. These results are 60 milliseconds (.006 second) better than the improvements made by the active control group. While statistically significant at a p value of less than .001, the difference of 60 milliseconds between the active group and the controls represents an incomprehensibly small amount. The result would appear to be significant but substantively meaningless.

There are numerous problems with how the IMPACT study was reported in the published article.<sup>54</sup> The study reported that the Brain Fitness Program intervention training effects transferred from auditory processing speed to

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<sup>53</sup> See Table 2, *ibid.*, 599.

<sup>54</sup> *Ibid.*



attention and memory tasks, a finding never before shown. This finding is based on the composite index score which the authors admit starts at close to the ceiling, with little room for improvement. The magnitude of improvement in other measures showing significantly better performance by the experimental group over the controls is difficult to interpret because the total possible scores are not provided. The study reported only change from mean baseline scores, not specific neuropsychological scores by person or group, making it difficult to evaluate results. The range of possible scores on the scales was not provided. In addition, the IMPACT study population was less diverse than the ACTIVE group, with Caucasians comprising 93.8% of the experimental condition and 95.5% of the active control, and both groups were well educated. The authors themselves state that the study population may limit the generalizability of the results. The active intervention offered, instruction in fields such as “history, art, and literature” sound problematic on the face, appealing perhaps only to a small subsection of the population who would be interested in these school subjects and therefore as fully cognitively engaged in such an intervention as in a game-type computer activity. Lastly, as with the ACTIVE trial, the IMPACT trial showed conflicts of interest, as the study was sponsored by Posit Science Corporation and author Henry M. Mahncke owns Posit stock and had input into the study design. The article does state that the principal investigators were Drs. Smith and Zelinski who did not work or own stock in Posit Science, perhaps reducing any conflict of interest. In general, however, the evidence for the IMPACT study appears to be very weak.

## Vascular Links

It appears that a breakdown in the integrity of discrete disease categories is central to the shift from thinking about Alzheimer's disease cures to thinking about cognitive health promotion in vascular terms. The Diagnostic and Statistical Manual of Mental Disorders, for example, classifies Alzheimer's disease and vascular dementia as separate diseases, the most and second most common causes of dementia, respectively.<sup>55</sup> Under this traditional classification system, Alzheimer's is a neurodegenerative disease, affecting neurons, and vascular dementia is a consequence of heart disease, affecting the blood vessels of the brain. Traditional estimates attribute about half of all dementia cases to Alzheimer's disease.<sup>56</sup> However, there is no consensus on exact numbers and there is some evidence the categorical estimates are in flux. A recent study conducted at the Veteran's Affairs, for example, found that only 30-50% of its veteran population had Alzheimer's disease and that the balance was shifting towards vascular-type dementias.<sup>57</sup>

In 1997 the Nun Study, a longitudinal study of aging and Alzheimer's disease, reported that the presence of vascular infarcts in brains with significant Alzheimer's pathology in autopsy corresponded with poorer cognitive function in life. The researchers concluded that "a few small infarcts in strategic regions of

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<sup>55</sup> American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR Fourth edition* (text revision) (Washington, D.C.: American Psychiatric Association, 2000).

<sup>56</sup> The Alzheimer's Association claims that AD accounts for 60-80% of cases. See Alzheimer's Association, "2012 Alzheimer's Disease Facts and Figures," *Alzheimer's & Dementia* 8, no. 2. (2012): 131-68.

<sup>57</sup> Elliot D. Ross, Santosh N. Shah, Calin I. Prodan, and Marilee Monnot, "Changing Relative Prevalence of Alzheimer Disease versus Non-Alzheimer Disease Dementias: Have We Underestimated the Looming Dementia Epidemic?" *Dementia and Geriatric Cognitive Disorders* 22, no. 4 (2006): 273-277.

the brain may be sufficient to produce dementia in those made vulnerable by abundant neuropathological lesions of AD in the neocortex. Alternatively, it is possible that our findings have less to do with the location of the infarct and more to do with the disease process that produce the lacunar infarcts,”<sup>58</sup> i.e., vascular disease. These findings help explain the previously mentioned paradox, also mentioned by these researchers, that the presence of neuropathologic lesions of AD (i.e., amyloid plaques and neurofibrillary tangles) do not necessarily correspond with dementia, that there may be brain or cognitive reserve that protects against functional deficits even with pathology unless that reserve is depleted or overwhelmed by comorbidities. In other words, even if Alzheimer’s disease represents a distinct neurodegenerative process, it often co-occurs with vascular disease (47% of the time in this sample), and it often seems to be the presence of the latter that unmasks the functional symptoms of Alzheimer’s.

Other researchers have noted the simultaneous presence of vascular factors and Alzheimer’s disease, including Alois Alzheimer himself who observed three elements in the brain of the first Alzheimer’s case in 1907: senile plaques and neurofibrillary tangles (new elements) as well as arteriosclerotic changes.<sup>59</sup> The arteriosclerotic element was dropped by Alzheimer’s colleague Gaetano Perusini in his description of Auguste D. as the first case in an article making the case for the new disease category in 1909.<sup>60</sup> The Rotterdam Study is credited

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<sup>58</sup> David A. Snowdon et al., “Brain Infarction and the Clinical Expression of Alzheimer Disease: The Nun Study,” *JAMA* 277, No. 10 (March 1997): 813-817.

<sup>59</sup> See Konrad Maurer, Stephan Volk, and Hector Gerbaldo, “The History of Alois Alzheimer’s First Case,” in *Concepts of Alzheimer Disease: Biological, Clinical, and Cultural Perspectives*, edited by Peter J. Whitehouse, Konrad Maurer, and Jesse F. Ballenger (Baltimore: The Johns Hopkins University Press, 2000), 5.

<sup>60</sup> *Ibid.*, 25.

with associating atherosclerosis with Alzheimer's disease in a paper in 1997, including showing a particularly strong interaction between the presence of the apolipoprotein-E epsilon 4 allele genotype associated with late-onset Alzheimer's and atherosclerosis.<sup>61</sup> One neuropsychologist, Jack C. de la Torre, has gone so far as to call for a paradigm shift to reclassify AD as a vascular disorder.<sup>62</sup> Marcus Richards and Carol Brayne call for AD to be considered a syndrome rather than a disease because of overlapping disease boundaries.<sup>63</sup> Those and similar calls opened the subject to exploration of lifestyle interventions used for vascular health.

In an interview, neurologist Peter Whitehouse summarized the blurring of disease boundaries from his perspective as producing indistinct combinations of Alzheimer's, vascular factors, Lewy bodies, and other physical changes associated with the functional outcome of dementia.<sup>64</sup> If combinations of pathologies are present, we need to ask, what is it that matters most? While there is no clear answer, an argument can be made that in a blend of Alzheimer's disease and

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<sup>61</sup> Albert Hofman et al., "Atherosclerosis, Apolipoprotein E, and Prevalence of Dementia and Alzheimer's Disease in the Rotterdam Study," *The Lancet* 349, no. 9046(1997): 151-154.

<sup>62</sup> See Jack de la Torre, "Alzheimer's Disease: How Does It Start?" *Journal of Alzheimer's Disease* 4, no. 6 (2002): 497-512, and Jack de la Torre, "Vascular Basis of Alzheimer's Pathogenesis," *Annals of New York Academy of the Sciences* 977 (2002): 196-215.

<sup>63</sup> Marcus Richards and Carol Brayne, "What Do We Mean by Alzheimer's Disease?" *BMJ* 341(2010): 865-867. If Alzheimer's is a syndrome, we are really talking about the syndrome of geriatric dementia. Such a perspective is represented by Peter Whitehouse, interview by author, telephone, September 19, 2011: "This is dementia. It's hard for people to realize that it's dementia."

<sup>64</sup> "[W]e thought we would be able to completely say that there's such a thing as Alzheimer's, such a thing as vascular dementia, such a thing as frontal lobe dementia, such a thing as Lewy body. Any literature you look at there's a huge overlap between these things. We're more confused, in fact I just got asked to comment for ABC News on another study about the relationship between diabetes and dementia. Well, that's because vascular factors play a role in so-called Alzheimer's and it's just a matter of degree how much Parkinson's, how much frontal, how much Alzheimer's, et cetera, et cetera. So all of these studies, not only is it a continuum but it's also the continuum of pathologies to cross the different disease categories, which we think are discrete but which aren't." Peter Whitehouse, interview by author, telephone, September 19, 2011.

vascular dementia, the vascular factors matter most because they have been shown to be modifiable. One public health review enumerated associations between Alzheimer's disease and cardiovascular and cerebrovascular disease, strokes, hypertension, and high cholesterol, as well as diabetes, suggesting that these connections could justify a life course health promotion agenda that would be built around a multifaceted intervention involving modifiable risk factors such as dietary fat intake, obesity, type 2 diabetes, hypertension, and physical exercise.<sup>65</sup> As the disease connections proliferate the dementia picture gets more complex and the idea of cognitive health begins to look less complicated by comparison.<sup>66</sup>

The shift to primary prevention of cognitive decline suggested that public health might fairly easily target health behaviors known to prevent vascular risk factors. Supporting this approach are a number of epidemiological studies looking at the outcomes of dementia or lesser cognitive impairment that have found an association with high blood pressure in midlife, including the Framingham Heart Study,<sup>67</sup> the Honolulu-Asia Heart Study,<sup>68</sup> and an unnamed

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<sup>65</sup> Sandra K. Pope, Valorie M. Shue, and Cornelia Beck, "Will a Healthy Lifestyle Help Prevent Alzheimer's Disease?" *Annual Review of Public Health* 24 (2003):111-32.

<sup>66</sup> This may have been what geriatric psychiatrist Hugh Hendrie meant in part when he stated that health promotion "starts with an illness, in this case AD, then gets broader and broader with more and more illnesses involved, precursors are examined, such as MCI, cognitive decline, risk factors – and you regress that to cognitive health. It's a kind of reverse mirror to illness." Hugh Hendrie, interview by author, telephone, September 15, 2011. Dr. Hendrie is included here as a researcher but a passage from the interview will not be quoted because of an unfortunate malfunction of the digital recorder.

<sup>67</sup> Merrill F. Elias et al., "Untreated Blood Pressure Level Is Inversely Related to Cognitive Functioning: The Framingham Study," *American Journal of Epidemiology* 138, no. 6 (1993): 353-364.

<sup>68</sup> See Lenore J. Launer et al., "The Association between Midlife Blood Pressure Levels and Late-Life Cognitive Function," *JAMA* 274, no. 23 (1995): 1846-51; Esther S.C. Korf, Lon R. White, Philip Scheltens, and Lenore J. Launer, "Midlife Blood Pressure and the Risk of Hippocampal Atrophy: The Honolulu Asia Aging Study," *Hypertension* 44, no. 1 (2004): 29-34.

study from Uppsala, Sweden.<sup>69</sup> At least three randomized controlled trial intervention studies have looked at the effect of lowering hypertension with drug treatment to prevent cognitive impairment, with positive results. But because these trials are extremely short relative to the pathological course of cognitive decline or heart disease, are usually conducted exclusively with people with cardiovascular disease or hypertension, and often start later in life, they do not seem to be suitable evidence for primary prevention despite positive results.<sup>70</sup> It can also be noted that these same limitations apply to two earlier studies not showing an effect of drug treatment on cognition.<sup>71</sup> However, both of these latter studies were intent on noting that there was no *harm* in lowering blood pressure in people later in life. This finding spoke to concerns that low blood pressure late in life is often associated with cognitive decline. That these studies show inverse relation between blood pressure level and cognitive performance is not sustained late in life is thought to be because of the effects of the neurodegenerative and vascular diseases on blood pressure. This finding further suggests a possible need to intervene before hypertension is established. The Framingham Study

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<sup>69</sup> Lena Kilander et al., "Hypertension Is Related to Cognitive Impairment: A 20-Year Follow-up of 999 Men," *Hypertension* 31, no. 3 (1998): 780-786.

<sup>70</sup> For example: 1) Francoise Forette et al., "The Prevention of Dementia with Antihypertension Treatment: New Evidence from the Systolic Hypertension in Europe (Syst-Eur) Study," *Archives of Internal Medicine* 162, no. 18 (2002): 2046-2053; 2) P Trenkwalder, "Potential for antihypertensive treatment with an AT1-receptor blocker to reduce dementia in the elderly," *Journal of Human Hypertension* 16 (2002): S71-S75, and 3) The PROGRESS Collaborative Group, "Effects of Blood Pressure Lowering with Perindopril and Indapamide Therapy on Dementia and Cognitive Decline in Patients with Cerebrovascular Disease," *Archives of Internal Medicine* 163, no. 9 (2003): 1069-1075.

<sup>71</sup> Martin J. Prince, Anne S. Bird, Robert A. Blizard, and Anthony H. Mann, "Is the Cognitive Function of Older Patients Affected by Antihypertensive Treatment? Results from 54 Months of the Medical Research Council's Treatment Trial of Hypertension in Older Adults," *BMJ* 312, no. 7034 (1996):801-805; William B. Applegate et al., "Impact of the Treatment of Isolated Systolic Hypertension on Behavioral Variables: Results from the Systolic Hypertension in the Elderly Program," *Archives of Internal Medicine* 154, no. 19 (1994):2154-60.

showing that untreated hypertension in midlife correlates with poor cognitive function later in life seems to be the best evidence for this early intervention.

In addition to being independently associated with cognitive outcomes such as Alzheimer's disease, vascular conditions frequently influence cognitive health directly. The Framingham Study found a significant 3.7-point drop in the mean Mini-Mental State Exam score in stroke patients within 6 months of having a large, left-sided stroke, as compared with no change in controls.<sup>72</sup> Another group found that 35.2% of stroke survivors were cognitively impaired, as opposed to 3.8% of controls, and that of those that were cognitively impaired, 55% were having functional consequences such as the inability to live independently.<sup>73</sup> Aside from recommending the lowering of hypertension to reduce risk of vascular dementia or Alzheimer's disease, one could recommend it to prevent atrial fibrillation, or sluggish blood flow, that can decrease flow of blood to the brain or precipitate the formation of blood clots and stroke. Hypertension has been shown to alter cerebral blood vessel structures, facilitating vascular occlusion and compromising cerebral perfusion.<sup>74</sup> According to the CDC, high blood pressure and heart failure are also risk factors for atrial fibrillation,<sup>75</sup> which diminishes

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<sup>72</sup> C. S. Kase et al., "Intellectual Decline After Stroke: The Framingham Study," *Stroke* 29, no. 4 (1998): 805-812.

<sup>73</sup> T K Tatemichi et al., "Cognitive Impairment after Stroke: Frequency, Patterns, and Relationship to Functional Abilities," *Journal of Neurology, Neurosurgery, and Psychiatry* 57, no. 2 (1994):202-207.

<sup>74</sup> See Franco Veglio, Cristina Paglieri, Franco Rabbia, Daniela Bisbocci, Mauro Bergui, and Paolo Cerrato, "Hypertension and Cerebrovascular Damage," *Atherosclerosis* 205, no. 2 (2009): 331-341.

<sup>75</sup> See Centers for Disease Control and Prevention, "Atrial Fibrillation Fact Sheet," Division for Heart Disease and Stroke Prevention website, [http://www.cdc.gov/dhdsdp/data\\_statistics/fact\\_sheets/fs\\_atrial\\_fibrillation.htm](http://www.cdc.gov/dhdsdp/data_statistics/fact_sheets/fs_atrial_fibrillation.htm) (accessed October 21, 2012).

perfusion. Modifiable risk factors for heart failure include smoking, being overweight, a high-fat diet, high cholesterol, a salty diet, and physical inactivity.<sup>76</sup>

A non-drug intervention that has received official sanction to lower hypertension is physical activity. As far back as 1996 the NIH held a Consensus Conference on Physical Activity and Cardiovascular Health and set a guideline of 30 minutes moderate-intensity physical activity on most days of the week for cardiovascular health, including high blood pressure. The statement noted that physical activity has secondary preventive effects (it “modifies” high blood pressure and thereby helps prevent cardiovascular disease) but also primary prevention effects (“Most studies of endurance exercise training of individuals with normal blood pressure and those with hypertension have shown decreases in systolic and diastolic blood pressure.”) The statement further attributed improved insulin sensitivity to endurance exercise.<sup>77</sup> The 2004 *U.S. Guide to Clinical preventive services*, Second Edition, included a section that recommended that physicians counsel patients to engage in regular physical activity, preferably daily, “to prevent coronary heart disease, hypertension, obesity, and diabetes. This recommendation is based on the proven benefits of regular physical activity....”<sup>78</sup> The report further suggests that physical activity can consist of everyday tasks of moderate intensity such as raking leaves,

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<sup>76</sup> See Centers for Disease Control and Prevention, “Heart Failure Fact Sheet,” Division for Heart Disease and Stroke Prevention website, [http://www.cdc.gov/dhdsp/data\\_statistics/fact\\_sheets/fs\\_heart\\_failure.htm](http://www.cdc.gov/dhdsp/data_statistics/fact_sheets/fs_heart_failure.htm) (accessed October 21, 2012).

<sup>77</sup> Russell V. Luepker et al., “Physical Activity and Cardiovascular Health: NIH Consensus Development Panel on Physical Activity and Cardiovascular Health,” *JAMA* 276, no. 3 (1996): 241-6. Note that the health promoter Lester Breslow was on the panel for this conference.

<sup>78</sup> U.S. Preventive Services Task Force, “Section 55 Counseling to Promote Physical Activity,” in *Guide to Clinical Preventive Services, Second Edition* (Washington, DC: U.S. Department of Health and Human Services, 1996) <http://odphp.osophs.dhhs.gov/pubs/guidecps/default.htm>, (accessed October 10, 2012).



cleaning windows, and light restaurant work for a duration of 60 minutes or everyday tasks of vigorous intensity such as shoveling snow for a duration of about 20 minutes.

Today CDC's Stroke page points visitors to a brochure called "Know the Facts about Stroke," which says that one of the signs and symptoms of stroke is "Sudden confusion or trouble speaking or understanding others" but does not anywhere mention any long-term cognitive effects of stroke that might give the concerned added reason for engaging in preventive behavior. The only apparent consequence of stroke is death (rather than years of chronic disability). The focus of the page seems to be on recognizing symptoms in order to get immediate treatment for stroke, but there is also a section "Can it be prevented?" that takes the long view and recommends to "Prevent or treat your other health conditions, especially high blood pressure, high cholesterol, and diabetes." The linked page on HBP states under "What you can do" includes the advice: "How to Prevent HBP: • Eat a healthy diet ... Avoid sodium by limiting amount of salt you add to food."<sup>79</sup> The CDC's Sodium Fact Sheet presents research on how low sodium both lowers blood pressure in both those with high and normal blood pressure, suggesting a long-term social benefit,<sup>80</sup> as blood pressure tends to rise with age. Given this officially sanctioned advice, it seems a small step to recommend lowering salt intake and encouraging physical activity to promote cognitive health as well as vascular health.

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<sup>79</sup> Centers for Disease Control and Prevention, "Know the Facts about Stroke," Division for Heart Disease and Stroke Prevention website, [http://www.cdc.gov/stroke/docs/ConsumerEd\\_Stroke.pdf](http://www.cdc.gov/stroke/docs/ConsumerEd_Stroke.pdf) (accessed October 5, 2012).

<sup>80</sup> Centers for Disease Control and Prevention, "Sodium Fact Sheet," [http://www.cdc.gov/dhdsp/data\\_statistics/fact\\_sheets/fs\\_sodium.htm](http://www.cdc.gov/dhdsp/data_statistics/fact_sheets/fs_sodium.htm) (accessed October 5, 2012).

## **Physical activity**

In addition to the endorsements for physical activity as a way to maintain healthy cognitive function indirectly through heart health, some researchers have worked on showing the direct benefit of physical activity on cognition. Dr. Art Kramer of the University of Illinois at Urbana-Champaign was one of the earliest and most steadfast researchers on the subject. Dr. Kramer's lab at the Beckman Institute for Advanced Science and Technology has been studying the effect of exercise on cognitive functioning in healthy older adults for some time. In a study published in 1999,<sup>81</sup> the group found that a six-week intervention randomly assigned to adults age 60-75 years old who reported having sedentary lifestyles to either walking (aerobic) or stretching and toning (anaerobic) intervention groups. The walking group showed a significant improvement first in the maximum rate of oxygen consumption compared with the control group (an increase of 5.1% compared with a decline of 2.8% in the control group). It then found improvements in three exercises that have been associated with executive control processes involving attention such as working memory, inhibiting distractions, and everyday tasks such as scheduling. Following the intervention, reaction times decreased significantly for only the exercise group on a test involving switching between tasks and on a test with distracter interference. These results are impressive because they represent a transfer of the training effect from the domain of physical exercise to cognitive

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<sup>81</sup> See Arthur F. Kramer et al., "Ageing, Fitness and Neurocognitive Function," *Nature* 400, no. 6743 (1999): 418-49.

function, specifically executive function tasks that involve planning and attention. However, the study had only 127 subjects, previously sedentary adults age 60-75 years old. In addition, lab-based tests of executive function are not necessarily everyday tasks or signs of health out in the community.

In more recent publications Kramer and colleagues recommend aerobic fitness training for brain health but admit that “at present we know little about how to design exercise interventions that optimize the effects on cognition and brain health.”<sup>82</sup> The authors recommend further research to determine the type, dose, frequency of exercise activities and when in life it is best to begin. They also point out that they do not know how exercise is able to boost cognitive functioning in both children and adults when the two groups are at such different stages of brain development. However, the *black box paradigm*, which allows for an exposure-outcome conclusion without understanding of the mechanism, has been an acceptable part of public health since the later 20<sup>th</sup> century.<sup>83</sup> From a practical perspective, it may be more important to know that something is effective than to know how the mechanism works.

### **Social engagement**

The NIH State of the Science Report devoted one line to social engagement in connection with cognitive health: “No good quality systematic reviews or RCTS were identified that evaluated a social engagement intervention to improve

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<sup>82</sup> See Charles H. Hillman, Kirk I. Erickson and Arthur F. Kramer, “Be Smart, Exercise Your Heart: Exercise Effects on Brain and Cognition,” *Nature* 9, no. 1 (2008): 63.

<sup>83</sup> See Mervyn Susser and Ezra Susser, “Choosing a Future for Epidemiology: I. Eras and Paradigms,” *American Journal of Public Health* 86, no. 5(1996): 668-673.

or maintain cognitive ability or function.”<sup>84</sup> Based on the report finding, the category of social engagement was not included in the NIH Conference statement for question 4: *What are the therapeutic and adverse effects of interventions to improve or maintain cognitive ability or function?*<sup>85</sup> Research into the connection between social networks and health is a major theme in the field of social epidemiology.

If we consider social epidemiology as “the branch of epidemiology that studies the social distribution and social determinants of states of health,”<sup>86</sup> social networks and social support are exposures that influence health outcomes. Larger, supportive networks are thought to be associated with better health outcomes and smaller weaker networks and especially social isolation with worse outcomes. The presence of social ties has been associated with longevity<sup>87</sup> and other health outcomes such as improved cardiovascular function, neuroendocrine function, immune function, lower inflammation, with mental health.<sup>88</sup> Increasingly, it is also associated with better cognitive health across the life course and at the end of life.

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<sup>84</sup> Duke Evidence-based Practice Center, *Preventing Alzheimer’s Disease and Cognitive Decline: Evidence Report/Technology Assessment No. 193*, AHRQ Publication No. 10-E005 (Rockville, MD: Agency for Healthcare Research and Quality, 2010), 281.

<sup>85</sup> Martha L. Daviglius et al., “National Institutes of Health State-of-the-Science Conference Statement: Preventing Alzheimer’s Disease and Cognitive Decline,” 14-16.

<sup>86</sup> Lisa F. Berkman and Ichiro Kawachi, *Social Epidemiology* (Oxford: Oxford University Press, 2000):6.

<sup>87</sup> Lisa F. Berkman and S. Leonard Syme, “Social Networks, Host Resistance, and Mortality: A Nine-Year Follow-up Study of Alameda County Residents,” *American Journal of Epidemiology* 109, no. 2 (1979): 186-204; James S. House, Karl R. Landis, and Debra Umberson, “Social Relationships and Health,” *Science, New Series* 241, no. 4865 (1988): 540-545.

<sup>88</sup> Bert N. Uchino, “Social Support and Health: A Review of Physiological Processes Potentially underlying Links and Disease Outcomes,” *Journal of Behavioral Medicine*, 29, no. 4 (2006): 377-387; Patrick Callaghan and Jean Morrissey, “Social Support and Health: A Review,” *Journal of Advanced Nursing* 18, no. 2 (1993): 203-210.

Berkman et al. offer a useful conceptual framework that put social networks in a larger social perspective.<sup>89</sup> According to the model, social networks are shaped by social-structural conditions at the macro level, including politics, socioeconomic factors, social change, and culture. Social networks, in turn, enable psychosocial mechanisms at the micro level, such as social engagement, person-to-person contact, access to material goods, forms of social support including information, and social influence. These psychosocial mechanisms operate on behavioral, psychological, and physiologic pathways in the body to induce health or ill health. Social networks themselves are usually quantified in the research, as in this model, in two broad dimensions: *structure* (including size, range, density, and other characteristics) and *characteristics*, which might be renamed intensity (including frequency of contact, duration, intimacy, reciprocity, among other things).

Although social epidemiological researchers have looked at family size and marital status, I will focus now just on social stimulation through general social and civic or cultural networks.

### Friends and relatives

A number of studies have linked lack of friends to cognitive decline with age.<sup>90</sup> Sometimes termed social isolation or social disengagement, having a poor

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<sup>89</sup> See Figure 7-1, Lisa F. Berkman and Thomas Glass, "Social Integration, Social Networks, Social Support, and Health," in ed. Lisa F. Berkman and Ichiro Kawachi, *Social Epidemiology* (Oxford: Oxford University Press, 2000): 143.

<sup>90</sup> Ariel F. Green, George Rebok, G., and Constantine G. Lyketsos, "Influence of Social Network Characteristics on Cognition and Functional Status with Aging," *International Journal of Geriatric Psychiatry*, 23, no. 9 (2008): 972-978; Deborah E. Barnes et al. "Women Who Maintain Optimal Cognitive Function into Old Age," *JAGS*, 55, no. 2 (2007): 259-264; Maria-Victoria Zunzunegui, Beatriz E. Alvarado, Teodoro Del Ser, and Angel Otero, "Social Networks, Social Integration, and Social Engagement Determine Cognitive Decline in Community-Dwelling Spanish Older Adults," *The Journals of Gerontology Series B Psychological Sciences and Social*

social network is negatively correlated with cognitive health. In the Established Populations for Epidemiologic Studies of the Elderly (EPESSE) cohort study, Bassuk, Glass, and Berkman<sup>91</sup> found that the odds of incident cognitive decline for seniors reporting no social ties at baseline was 2.24 that of people reporting ties over a three-year period, 1.91 over a six-year period, and 2.37 over a twelve-year period.

Other studies are bolder in asserting that larger social networks correlate with better cognitive health, suggesting a protective effect over time. Social networks were positively correlated with “slower” or “delayed” cognitive decline according to several researchers.<sup>92</sup> The Women’s Memory Study, which gathered annual data from female members of Kaiser Permanente Southern California asserted that from 2001 to 2005 women aged 78 and up were protected by a large social network.<sup>93</sup> People who had a composite network size of 12-30 people had a .74 hazard ratio for dementia over the study interval compared to people with a network size of 0-11, after adjusting for demographic and health conditions that are risk factors for dementia, a dichotomous cognitive score, and for hormone use at baseline. People who had a relatives network comprising 6-15 people had a .64 hazard ratio for dementia compared to people with 0-5 relatives in their network.

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*Sciences* 58B, no. 2 (2003): S93-S100; Shari S. Bassuk, Thomas A. Glass, and Lisa F. Berkman, “Social Disengagement and the Incident Cognitive Decline in Community-Dwelling Elderly Persons,” *Annals of Internal Medicine* 131, no. 3 (1999): 165-173.

<sup>91</sup> Bassuk, Glass, and Berkman, “Social Disengagement and the Incident Cognitive Decline in Community-Dwelling Elderly Persons.”

<sup>92</sup> Karen A. Ertel, Maria M. Glymour, and Lisa F. Berkman, “Effects of Social Integration on Preserving Memory Function in a Nationally Representative US Elderly Population,” *American Journal of Public Health* 98, no. 7 (2008): 1215-1220; L. L. Barnes et al., “Social Resources and Cognitive Decline in a Population of Older African Americans and Whites,” *Neurology* 63, no. 12 (2004): 2322-2326.

<sup>93</sup> Valerie C. Crooks et al., “Social Network, Cognitive Function, and Dementia Incidence among Elderly Women,” *American Journal of Public Health* 98, no. 7 (2008): 1221-1227.

People who had 6-15 friends in their network had a .85 hazard ratio for dementia than people with 0-5 friends. In this study, relatives in one's network reduced dementia risk more than friends. In addition to network size, daily contact with network members was found to almost halve the hazard ratio for dementia. Of concern in this study, as in many others, is the crudeness of the instrument that measures cognition. In this case the 23-question Telephone Interview for Cognitive Status-modified was used, similar to the Mini-Mental Status Examination (MMSE), which often sorts people into demented and non-demented statuses rather than measuring people along a wider continuum.

Holtzman et al.<sup>94</sup> found a link between large social networks at baseline for people aged 50 and up and better MMSE status twelve years later, but they concluded that larger social networks were an “indicator” not a determinant of cognitive health. This more conservative depiction of the findings seems appropriate given the lack of life course data for these studies and because of the difficulty in establishing directionality of exposure to health outcome. Saczynski et al.<sup>95</sup> reported no significant association between midlife level of social engagement and cognitive status in old age in the Honolulu-Asia Aging Study, although they did find that a decrease in social engagement was associated with cognitive decline. These authors suggest that previously researchers who found a protective effect for forms of social engagement were assuming rather than establishing that social networks precede cognitive health. Cognitive health could just as easily enable social networks.

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<sup>94</sup> Ronald E. Holtzman et al., “Social Network Characteristics and Cognition in Middle-aged and Older Adults,” *The Journals of Gerontology* 59B, no. 6 (2004): P278-P284.

<sup>95</sup> Jane S. Saczynski et al., “The Effect of Social Engagement on Incident Dementia: The Honolulu-Asia Heart Study,” *American Journal of Epidemiology* 163, no. 5 (2006): 433 -440.

One study that addressed the directionality issue was the Rush Memory and Aging Project. The advantage of this large longitudinal study is that brain autopsies were conducted at death to determine Alzheimer's pathology. Post-mortem data for the first 89 people who have died suggested that those with larger social network sizes in life had better cognitive results even if they possessed heavier global disease pathology.<sup>96</sup> Network size was quantified by number of children, family, and friends that the study participants saw monthly. Consistent with the cognitive reserve hypothesis, the findings of the Rush study offer promise of establishing a stronger case for behavior modification that involves building larger, more supportive social networks to protect and enhance cognitive health with age.

One group of researchers objected to the use of social structures as proxies for *social interaction* because it assumes that interaction is happening within these structures. They designed a randomized control experiment (n=76) to test the effects of a social interaction intervention and found that as little as a 10-minute discussion of a social issue had a similar effect on cognitive performance (processing speed and working memory) as 10 minutes of engaging in intellectual activities on one's own (reading, doing a crossword puzzle, doing a mental rotation task) and was significantly more effective than the 10 minutes of

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<sup>96</sup> David A. Bennett et al., "The Effect of Social Networks on the Relation between Alzheimer's Disease Pathology and Level of Cognitive Function in Old People: A Longitudinal Cohort Study," *Lancet Neurology* 5, no. 5 (2006): 406-412.



television watching performed by controls. However, the age range of the study participants was 18-21 and so it is not applicable to an older population.<sup>97</sup>

Although some findings on social networks suggest that number of interactions has a stimulating, healthful effect on the brain even when those interactions are tense and demanding, a few researchers insist that it is the supportive quality of the network not its sheer size or frequency that matters. The Kungsholmen Project found that infrequency of contact with a network did not affect cognition if the contact was judged to be satisfying.<sup>98</sup> In contrast to other studies, an analysis of the MacArthur Studies of Successful Aging found that greater frequency of emotionally supportive interactions with all types of network members was inversely correlated with cognitive decline over a 7.5-year period, but that presence of social ties was not.<sup>99</sup>

Several longitudinal studies found only weak or insignificant associations between social ties and cognitive health.<sup>100</sup> Clearly much more work needs to be done to scrutinize the possible causal relations between social engagement with friends and family and late-life cognitive health.

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<sup>97</sup> Oscar Ybarra et al., "Mental Exercising through Simple Socializing: Social Interaction Promotes General Cognitive Functioning," *Personality and Social Psychology Bulletin*, 34, no. 2 (2008): 248-259.

<sup>98</sup> Laura Fratiglioni et al., "Influence of Social Network on Occurrence of Dementia: A Community-based Longitudinal Study," *The Lancet* 355, no. 9212 (2000): 1315-1319.

<sup>99</sup> Teresa E. Seeman, Tina M. Lusignolo, Marilyn Albert, and Lisa Berkman, "Social Relationships, Social Support, and Patterns of Cognitive Aging in Healthy, High-Functioning Older Adults: MacArthur Studies of Successful Aging," *Health Psychology* 20, no. 4 (2001): 243-255.

<sup>100</sup> Green, Rebok, and Lyketsos, "Influence of Social Network Characteristics on Cognition and Functional Status with Aging"; P. C. Elwood et al., "Smoking, Drinking, and Other Life Style Factors and Cognitive Function in Men in the Caerphilly Cohort," *Journal of Epidemiology and Community Health* 53, no. 9 (1999): 9-14; Marilyn S. Albert et al., "Predictors of Cognitive Change in Older Persons: MacArthur Studies of Successful Aging," *Psychology and Aging* 10, no. 4 (1995): 578-589.

### Civic or cultural networks

A number of studies include a “social engagement” or commensurate measure that assesses involvement in group activities beyond one’s personal network of friends,<sup>101</sup> yet these elements are rarely emphasized in analysis. Two studies only give prominence to the civic or cultural dimension of social networks and their connection with cognitive health in old age. A study of community-dwelling people aged 65 and up near Madrid found active engagement with a church, a senior center, park, or other group was positively correlated with better cognitive health over time.<sup>102</sup> The Caerphilly Study of men aged 55-69 found positive associations between social leisure activities such as sports or club attendance, community work, or cultural event attendance and cognitive health.<sup>103</sup> Given the inclusion of the variable, one would expect much more discussion and analysis in the literature. The fact that the two studies that emphasized civic and cultural engagement are European may be a tip-off that American studies may suffer from a cultural bias that is less interested in group or community activities and more interested in individual relations.

Altogether, the literature on modifiable lifestyle behaviors suggests possible public health opportunities to promote cognitive health in aging through

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<sup>101</sup> Sacynski et al., “The Effect of Social Engagement on Incident Dementia: The Honolulu-Asia Heart Study”; François Béland et al., “Trajectories of Cognitive Decline and Social Relations,” *Journals of Gerontology Series B Psychological Sciences and Social Sciences* 60B, no. 6 (2005): P320-P330; Barnes et al., “Social Resources and Cognitive Decline in a Population of Older African Americans and Whites”; Seeman et al., “Social Relationships, Social Support, and Patterns of Cognitive Aging in Healthy, High-Functioning Older Adults”; Bassuk, Glass, and Berkman, “Social Disengagement and the Incident Cognitive Decline in Community-Dwelling Elderly Persons.”

<sup>102</sup> Zunzunegui et al., “Social Networks, Social Integration, and Social Engagement Determine Cognitive Decline in Community-Dwelling Spanish Older Adults.”

<sup>103</sup> Elwood et al., “Smoking, Drinking, and Other Life Style Factors and Cognitive Function in Men in the Caerphilly Cohort.”

cognitive, physical, and social engagement across the life course. These opportunities are built around interdisciplinary ideas of enhancing cognitive reserve within neuropsychology, maximizing cognitive resources in developmental psychology, and in compressing morbidity within public health in the latter part of life.

## Chapter 3

### Methods

Using a grounded theory approach,<sup>1</sup> I interviewed active cognitive health experts in the United States and examined their arguments made for or against public health recommendations. These experts included some of the participants of both the HBI and the State-of-the-Science Conference (e.g., Indiana University geriatric psychiatrist Hugh Hendrie). During interviews I asked these experts to recommend other experts who informed public policy, using a snowball sampling method. For example, one HBI participant, Johns Hopkins University geriatric psychiatrist Peter Rabins recommended that I speak with a non-HBI participant, Case Western University neurologist Peter Whitehouse.

All of those interviewed and included in the analysis are briefly profiled in the **Appendix: Profiles of Cognitive Health Experts Interviewed**. In keeping with grounded theory research, the number of interviews was not set ahead of time but was determined to be complete when the same themes began to be repeated and “saturation” of argument themes was reached. In total, I conducted seven researcher interviews.

The project was reviewed by the Institutional Review Board Sociobehavioral Committee at Emory University and given exempt status. Nevertheless, I distributed a consent form that was signed by all interviewees indicating their voluntary participation of the project and their right to drop out at any time. The interviews were all conducted either in person or, where not

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<sup>1</sup> Barry G. Glaser and Anselm L. Strauss, *The Discovery of Grounded Theory: Strategies for Qualitative Research* (Chicago: Aldine Publishing Company, 1967).

possible, over the telephone. These interviews were usually one hour in length, but they ranged from 42 minutes to 2 hours and 21 minutes. I used a semi-structured protocol, with similar questions about the interviewee's work, their definitions of key terms related to cognitive health, their knowledge of the national cognitive health initiatives and events, and their assessment of evidence supporting for behavioral change for cognitive health. However, the conversations flowed according to unique points made by the interviewees, and points made influenced questions asked in subsequent interviews. The interviews were audio recorded and transcribed verbatim. Of the seven, one was not fully recorded due to a taperecorder malfunction and so will not be analyzed.<sup>2</sup>

Distilling arguments presented a second constant comparison process, involving perceiving elements, sorting them, and combining them where possible. I used the Toulmin model of analyzing arguments to examine textual or spoken discourse on cognitive health.<sup>3</sup> Stephen Toulmin was a British-born philosopher who emphasized applied over theoretical logic. Toulmin stated that any serious assertion made could be tested for its justificatory argument. He established a four-part pattern of analysis. First, the analyst identifies the argument's central claim. In his example of a scientific argument, this central claim might be the prediction of when a lunar eclipse would occur after September 6, 1956. Second, the analyst identifies evidence in support of the claim (for example, "*Observed positions of sun, moon and earth up to 6 September 1956*"). Third, the analyst articulates the "warrant," or rationale, that connects the evidence to the claim. In

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<sup>2</sup> Hugh Hendrie, interview by author, telephone, September 15, 2011.

<sup>3</sup> Stephen Toulmin, *The Uses of Argument* (Cambridge: Cambridge University Press, 1958).

this example, the warrant is “*current laws of planetary dynamics.*” Fourth, the analyst identifies the backing or evidence for the warrant. In this case, the backing for the warrant is determined to be the “*totality of experience on which the current laws are based up to 6 September 1956.*”<sup>4</sup>

While the claim is explicit, the warrant is usually implicit and needs to be analyzed and articulated in order to be evaluated. In addition, Toulmin distinguished between warrant-using arguments, or those that rely on established rationales (as in the example given above), and warrant-establishing arguments, or those that try to put forth new explanations for why evidence supports a claim. Warrant-establishing arguments are often used in scientific papers. A warrant-establishing argument related to the eclipse prediction might be, hypothetically, one that proposes a new law of planetary dynamics on which to base its prediction.<sup>5</sup>

Toulmin saw arguments that address a particular problem and share the same type of evidence and conclusions as comprising a “field of argument.” In his words, “If fields of argument are different, that is because they are addressed to different sorts of problems. A geometric argument serves us when the problem facing us is geometrical; a moral argument when the problem is moral; an argument with a predictive conclusion when a prediction is what we need to produce, and so on.”<sup>6</sup> I take from these words that even if arguments come from different disciplines, they can be brought together into a dialogue known as a “field of argument” if they address the same problem, such as behavior that can

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<sup>4</sup> Ibid., 184.

<sup>5</sup> Ibid.

<sup>6</sup> Ibid., 167.

maintain or improve cognitive health based on the evidence that can be warranted to support the claim. To take it even further, claims that are made addressing the same problem can be pressed for argument, and the resulting arguments will belong to the same field of argument. Toulmin likens the analysis of arguments to legal deliberations. Usually claims are under scrutiny but where the arguments are warrant-establishing, the warrant itself is “on trial.”<sup>7</sup>

The assertions made by cognitive health researchers can be analyzed according to argument. In order to do this, I felt it was necessary to select representative excerpts from important documents or interviews in order to capture the full array of arguments found. Using the Toulmin model, I lay out claims, evidence, warrants, and backing for each passage quoted that address whether public health recommendations can be made for cognitive health in older adults. For one argument, the *Evidence-Based Policy Argument*, the warrant is well established and the default rule (i.e., that randomized controlled trials are the only valid proof of the effectiveness of lifestyle behaviors for cognitive health). The rest of the arguments propose other warrants that challenge the established warrant, and these arguments are therefore warrant-establishing.

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<sup>7</sup> See *Ibid.*, 120, 135, for this discussion.

## Chapter 4

### Results

The main arguments made by researchers for or against public health recommendations for cognitive health can be distinguished by their epistemological warrants as was described earlier. There were four altogether: 1) the *Evidence-Based Policy Argument* (as presented by Leonard Poon and Jennifer Manly), 2) the *Epidemiologically Informed Policy Argument* (as presented by Yaakov Stern and Peter Rabins), 3) the *Triangulated Evidence Policy Argument* (as presented by George Rebok), and 4) the *Logically Derived Policy Argument* (as presented by Peter Whitehouse). This chapter addresses each individual argument in turn as derived from an interview excerpt and grouped by thematic content.

### Arguments for and against Cognitive Engagement

Though quite familiar with the ACTIVE Trial, Dr. Leonard Poon of the University of Georgia did not endorse a message of cognitive engagement. Poon raised a number of problems with the research to date from his vantage point as a cognitive aging psychologist. An excerpt from his interview follows:

#### Leonard Poon

...[T]he finding is very robust and reliable that there are [age-related cognitive] changes. The changes are not uniform: some changes are positive, some are negative. The slope of change definitely varies across individuals. [For example,] your wisdom, your experience, your accumulation of experience, your crystallized intelligence – that goes up with age. We know, on the other side, your fluid intelligence does go down with age and there are many reasons and it may not be because of the brain. It could be lack of practice.... It's just that you haven't exercised those kinds of skills



for a long time and all of the sudden you're confronted by someone asking you to perform those skills and immediately you can't get to it, but with a little bit of practice you can get back to your previous level. And so it doesn't have anything to do with the integrity of your brain but the context from which you're functioning....you may *lose interest* in these particular topics and therefore you're not up to date on it. But, on the other hand, you may be up to date on other areas that you should be able to perform at a high level because you've been in it for such a long time. And it is invariant of brain function.

Now the interesting thing about that study [ACTIVE], it really turns out that a lot of these techniques that purport to increase memory have very small effect sizes. And they also found, and it's confirmed in the literature, that there's lots of individual differences. Frequently, too, and this is not just jargon, the mean doesn't represent anyone. So I guess the issue is that when you talk about the aging brain and when you talk about cognition, you also need to talk about variability. And I think the study of variability perhaps is more important than the study of the phenomena median, mode, central tendency....Public health needs to be sensitive to individual variability, understanding the phenomena is such that it would not provide us with a simple definition. So I wouldn't say it would exclude public health, but public health has to understand that with cognition you're talking about the mind and you're also talking about so many things that would influence the mind and your measurement frequently is indirect, you know, it's not like any treatment is so strong that you're going to get a very uniform response. But I think it's important for public health to understand the variability issue. I think it's a front and center issue.

...[Evidence for lifestyle factors that can improve or maintain cognitive health,] I think it's really emerging. And it will probably be emerging as one of the key factors.... You know, for a long, long time people would say if you exercise your brain there's a good chance that you could either delay or escape from having Alzheimer's and your so-called brain would be healthier. And there were two review papers that came from Tim Salthouse and Margie Gatz, saying that the evidence is just not there if you have proper control of this. It's more self-fulfilling prophecy, it's more that if you put in a lot of effort, it *must* be good for my brain and therefore it is good. But it is difficult to get evidence of increased efficacy mostly because of this variability issue. So the area of cognition and aging, under some circumstances, is fairly easy, you know, that there are certain factors that are good or not good for that, but the test of intervention is very difficult. You can use that person as his own baseline, and if you do it longitudinally, to make sure that you have replication longitudinally to see indeed what the variation is.

The technique that I have advocated for a long long time is...called allometric analysis that compares the slope to a baseline.... it's more experimental, it's laboratory-based and it's not practical for clinical evaluation....Physicians and others want a very simple thing [assessment tool], like the MMSE [Mini Mental State Exam], and the MMSE doesn't really tell you too much. You could have a perfect MMSE and you can still be demented. That's true. Because the baseline of that person is so high, you get down to perfect because those items are so easy.... Cognition is not simple and if you want to have good diagnoses you have to spend time to do the diagnoses...There's a phenomenon called the complexity hypothesis and ... what the complexity hypothesis says is that when you increase complexity of task demand on both young people and old people, old people are disproportionately disadvantaged. And so when you are probing the performance of younger people, when you increase the complexity they get slower, they make more errors, so there's a slope. When you do the same thing to older people that slope is steeper. And that steeper slope could be estimated in normal aging. And then with pathology that slope increases.... I have done work that showed that in normal aging there is a statistically significant difference in slope in that older people are slowed by about 36%. And then I used the same measurement technique to take a look at what happened to both people who are demented but not depressed and depressed but not demented, and I got different slopes out of it.

...we do know that aging without disease shows different patterns of cognitive changes. And when you add pathology on top of that then the functioning would change because of the pathology. And it could be additive or multiplicative. So you have certain levels of change over time that are supposedly normal, and then when you have a stroke or whatever other things then you know that that would be on top of the normal changes. We don't know whether it's additive or multiplicative but certainly if you have pathology on top of the impact of time then you are certainly more disadvantaged. But there's lots of data sets that show that there are patterns of impact just due to time. And I think one can learn from those patterns and devise suggestions to delay those changes if at all possible.<sup>1</sup>

In interpreting this passage as an argument, we can deduce the claim that *We cannot yet issue public health recommendations for behavior change.* Dr. Poon provides many reasons for this claim. We do not have conclusive evidence

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<sup>1</sup> Leonard Poon, interview by author, Athens, GA, September 20, 2011.

because evidence for lifestyle factors such as cognitive engagement is still “emerging.” Mainly, however, researchers do not even seem to agree on how to measure cognition. We are at a very preliminary stage of agreeing on research variables. His own proposal to measure individual slopes of change against normed slopes of change for different conditions remains “experimental.”

In this discussion of measurement problems, Poon alludes to large disciplinary rifts between researchers. For example, there is a rift between psychology, an individual-based discipline, and public health, a population-focused discipline. We need to figure out how to separate cognitive factors from other psychological factors that have a bearing on individual “performance.” To draw on the performance metaphor, two actors with healthy brains might respond differently to sound, with one forgetting his lines in a setting that is overly noisy and the other forgetting them in a setting that is unsettlingly silent and still. An ideal performance takes practice, motivation, and a sense of comfort in the performance setting and would have different requirements based on life history and on personality. An introvert, for example, might be threatened by a performance situation where many other people are present, and an extrovert might be motivated in a setting where there is someone important to impress. Each person has a range of abilities and performs better or worse based on the compatibility of the context. To say that a test performance *is* that person’s cognition is problematic. Psychology has traditionally considered contextual factors around behavior that are highly individualized such as personality (introversion, extroversion, neuroticism, conscientiousness, interests, particular factors that stress an individual), history (for example, life experiences),

functional capacity (“baseline” functioning, which perhaps might also be termed intelligence, rate of change with age, presence of pathology), and perhaps also beliefs and culture (“if you put in a lot of effort, it *must* be good for my brain”), in addition to age. Poon emphasizes that measurements need to be built around change in the individual.

Another disciplinary rift is between psychology and clinical medicine. Both, he suggests, “diagnose” people, but psychologists will go in depth whereas physicians want a simple quick tool to diagnose dementia – the Mini-Mental State Exam (MMSE) – which is not sensitive enough for a health-based discussion as we are talking about. Another major issue touched upon is the difference between age-related change in cognition and pathology. Since “the slopes” are different between young and old, we might ask whether the first issue, age-related change is considered an important health issue. How many people in their concern about “cognitive decline” are talking about “normal” age-related change and how many are talking about pathology? If they are talking about “normal” age-related change, does it mean that it is a non-issue because it is not “pathological”? Is normal age-related change also a public health issue today?

Poon suggests the warrant that RCTs alone can support public health messaging. As ACTIVE is an RCT that lacks impact, we are not ready to issue lifestyle recommendations *en masse* for behavior change. In examining the evidence, Dr. Poon noted that the effect sizes for ACTIVE were very small. Dr. Poon’s second criticism of the ACTIVE study was that the study masked large individual differences in performance. In reading the results of this landmark article we are reading averages of all scores in the groups and how these means

change over a five-year period. We do not see the actual test scores or absolute numbers, nor do we see a median, and skewness has been removed.<sup>2</sup> In examining the data through Dr. Poon's perspective of variability, it seems that improvements in the reporting of IADL difficulty in the Reasoning group have more to do with the lower intra-individual variability within that group compared with the control group. The absolute numbers from baseline to five year measurement suggest that the control group improved much more than the reasoning group (a decline in difficulty of 1.2 for the control group vs. 0.4 by the reasoning group) with starting difficulties higher for the reasoning group than the control group. Effect size is defined as training improvement from baseline to year 5 for the intervention group minus improvement during the same period for the control group, divided by intrasubject standard deviation of the adjusted composite for the intervention group. Therefore, the significant result for the reasoning group seems to be coming from a smaller intrasubject variability number for this group. That in and of itself might be an interesting marker of uniform application in the reasoning intervention but it is a different finding from that reported in the ACTIVE study article. Without the right measurements we cannot make public health recommendations. Dr. Poon stays close to the *Evidenced-Based Policy Argument* in stating that we are not ready to issue lifestyle recommendations for cognitive health.

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<sup>2</sup> Willis et al., "Long-term Effects of Cognitive Training on Everyday Functional Outcomes in Older Adults."

Whereas Poon touched on the need to separate “normal” age-related change from contextual and pathological effects, Dr. George Rebok suggested that age-related change was an increasingly salient issue for the public and that this fact might play into conclusions one would draw based on evidence for lifestyle behavior for cognitive health. Below is an excerpt from his interview:

George Rebok

...[C]ognitive impairment is a very prevalent problem for older adults. And I think we live in a more complex society these days too, so the premium placed on cognition and the new roles for older adults, the changing roles, has sort of amplified the importance of cognitive health, not just for older people but for people in general. Buzz Hunt in Washington writes about ... not being smart enough for society, that with technological advances, the rapid pace of change, that we are not going to have the cognitive skills to master it. As people work longer, there's questions about maintaining cognition to be able to fulfill work roles.... I've noticed in my own studies, when I first started out, when I'd advertise for a study on cognitive health I got very few takers and nowadays you advertise for something to do with cognitive health, particularly if it involves an intervention, and people are sort of lining up at your doorstep.

...When we talk about cognitive health I think people are sort of looking for the magic bullet, they want *one* thing that they can do, if they can take *one* pill or they can do *one* crossword puzzle activity or they can sign up for one brain health program, or whatever it is, I think people are looking for a particular answer. And I guess I would suggest that, and I think it would be consistent with the HBI, that it really needs to be much more of a lifespan approach, it needs to be more curricularly based, that it's not going to boil down to one course or one training program or whatever – you think when you go to college you don't get just one course, you get a whole curriculum, and I think in cognitive health we need a curriculum of cognitive health. Most of these so-called brain training programs last much less than a typical college course in terms of the dosage that you get and so I think one of the messages has to be that you need to start early, you shouldn't wait until you're 60 or 65, that it's got to be a lifelong process, you need to start thinking of early protective factors around diet and exercise and good healthy lifestyle management, and then thinking about it in terms of multiple things that you can do to maintain your cognitive health. It's not going to come down to

doing just one mental exercise a day, just like you can't do just one physical exercise to be physically fit, it's got to be multifaceted.

...My sense was that there was really some evidence that's out there that was ignored or minimized in the final [State-of-the-Science Conference] report. There's a *huge* literature on cognitive training. We just completed a review on memory training going back to the 1960s and they're, just in the U.S. there are over 400 published articles on memory training and other aspects of cognitive training. There's a pretty substantial literature.... There was some mention of that evidence in there but I think, you know, that's been accumulating now for two, three decades and I didn't see any serious attempt made in that report to really look at that evidence....Everybody cites ACTIVE because that is sort of the gold standard in terms of cognitive training studies, but ACTIVE is certainly not the only training study that's ever been done, there's dozens and dozens....and I think the cumulative weight of the evidence, when you look even applying fairly stringent criteria, evidence-based criteria, still leads you in a somewhat different direction than in the consensus report.

... there's been skepticism about cognitive training and the degree of plasticity that exists. I think we place so much faith in pharmaceuticals and drug trials as going to provide sort of the answer here, and if you look at effect sizes, they're very small for drug trials, there's been a lot of failed drug trials, and I think that's another reason why I think there's much more interest in more behavioral kinds of approaches. But I think there's still skepticism about behaviorally based approaches that somehow don't involve some underlying physiological mechanism. I think for cognition it reflects sort of the medical view/model.

... I don't think the question is any longer if this stuff works. The answer to that is yes, it works. I think the more relevant question now is who does it work best for, under what circumstances does it work, for how long does it work, how can we introduce it into the population, even if we have these techniques how will they ever get injected into the population so that these procedures will become sort of institutionalized, really, within society. So we've got these programs out there but often seen as sort of gimmicks or the latest fad, people sometimes don't take this stuff seriously, you're selling me the latest memory trick, you're selling me this, you're telling me exercise is good or here's the fad diet, as long as I eat this I'm going to be cognitively healthy or whatever, so I think there's a lot of skepticism out there too.

...[In terms of additional evidence,] There's the IMPACT study, Elizabeth Zelinski and colleagues, IMPACT study, and that's another fairly large scale clinical trial of interventions that are based on interventions that were used in ACTIVE, at least one

that involved speed of processing which we found to be highly efficacious in ACTIVE. We're actually also doing a meta-review of computerized training programs for older adults, since that seems to be a new potential area for interventions. The number of studies is much smaller.

I think they're [the State-of-the-Science Statement is] behind the field here. I think the field has moved on. I think the questions are different than the questions they were raising.... There was a lot of disenchantment with the NIH report....I don't think we've really totally scraped the potential of the interventions. Most of the interventions we're talking about, like ACTIVE, are very short-term, limited interventions, you know, that are single ability focused or focused on a small number of abilities and so, what we're going to be seeing, I'm sure, in the future is more cross-training, sort of systems-level intervention where you combine like cognitive training with physical exercise with nutraceuticals with social engagement, doing models where we're actually combining - more of a curriculum kind of idea, getting back to what I said earlier, rather than thinking there is one cognitive training program focused on this ability is going to make a big difference, or we're going to do this for six weeks in the hopes that it will reverse a lifetime of health habits, and poor diet, and isolation.<sup>3</sup>

In this passage, Rebok appears to claim that *We can recommend cognitive engagement to the public for their cognitive health*. This claim represents a general rather than specific message. For evidence Rebok mentions over 400 studies since the 1960s that he has reviewed. He mentions ACTIVE trial as the recognized "gold standard" clinical trial. Rebok also pointed to the less-cited IMPACT Trial. As one of the principal investigators for the ACTIVE trial, Dr. Rebok noted its impact and effects. Though citing both ACTIVE and IMPACT as evidence for the efficacy of cognitive training, Dr. Rebok also acknowledged that they were short-term, limited interventions that focused on single cognitive abilities at a time. He also suggests that evidence might need to come from

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<sup>3</sup> George Rebok, interview by author, Baltimore, August 11, 2011.



studies on many different kinds of intervention studies because there is unlikely to be one behavioral “magic bullet.”

Rebok’s position that we are ready to encourage cognitive engagement based on the available evidence is supported by the warrant that the cumulative weight of evidence over time can suffice in the absence of more conclusive data. Rebok criticizes a more positivist paradigm that demands visual evidence of effect in noting the “skepticism about behaviorally based approaches that somehow don’t involve some underlying physiological mechanism.” Such a statement is probably a reference to cognitive reserve, which unlike brain reserve may refer to efficiency of brain usage (the brain’s so-called software as opposed to the brain’s so-called hardware).<sup>4</sup>

Rebok backs this warrant by pointing to a professional consensus with the words “I think they’re [the State of the Science Conference Statement] behind the field here. I think the field has moved on.” He also calls attention to the salience of the issue among the public as well as confusion around it.<sup>5</sup> In looking for a magic bullet, people are clearly impatient. In addition there is a need to use social capital that’s accumulated, and has the potential to do a lot of good as it

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<sup>4</sup> See, for example, Yaakov Stern, “What Is Cognitive Reserve? Theory and Research Application of the Reserve Concept,” *Journal of the International Neuropsychological Society* 8 (2002): 448-460.

<sup>5</sup> Elsewhere in the interview, Rebok says, “I think people in general are confused now, the public in general is confused because they don’t know who to really listen to, what the data are really telling us, should I do this, take this vitamin, or eat these foods, do this and your brain will stay happy. I think it’s confusing, it’s confusing for experts in the field to really know where the field’s at. I can only imagine what it must be like if you have no background in this area and are listening to some show on cognitive health or are reading something in a popular magazine. There needs to be almost like a clearinghouse of not only just what works in terms of cognitive health promotion but what the public will accept.” *Ibid.*

will encourage a generally healthy society whether it be through health behaviors or volunteerism.<sup>6</sup>

By pooling evidence across studies and even across behaviors (assuming that cognitive engagement would only account for part of the health effect because he too suggests that the effect sizes for each behavior may be too small to be the only thing one could do and that instead “we need a curriculum of cognitive health”) we can meet some public demand while continuing to refine the message. Ultimately, in offering evidence for cognitive training, Dr. George Rebok presents a *Triangulated Evidence Policy Argument* in support of public health messages for behavior change.

Dr. Yaakov Stern was the last interviewee to address the evidence available to support a public health message for cognitive engagement for cognitive health.

An excerpt from his passage follows:

Yaakov Stern

...I think that it's fair to say that epidemiology really supports the idea that there's a set of life exposures that seem to promote, in my parlance, cognitive reserve and healthy aging. On the other hand, I don't think that we can give people a specific recipe/prescription with confidence. Let's put it this way. I don't think you can say, look, if you play Sudoku every night, or you take an adult course, or if you run and do crossword puzzles you're going to do better. I think anyone who says that with confidence is probably off-base. On the other hand, I think we

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<sup>6</sup> “I think cognitive health involves broader concepts in terms of things like societal engagement, civic engagement, that you're doing things that benefit society, more of an altruistic maybe kind of a focus, and I think that's one of the problems with a lot of interventions that are done to improve cognitive health, is that the focus is too narrow, on the individual, and that we appeal to people's fears about their declining memory or some other ability that may be declining as they grow older, and so it's very sort of individualistic, but I think we really need to think more at the population level, we need to think about cognitive health as maybe appeals to people wanting to see a better society, wanting to be remain engaged in society, wanting to give back to society. There are interventions that lead to sort of how do we create what I call and a lot of people call social capital in society, you know groups of people with sort of a collective sense of health and efficacy and the ability to really make a difference in the world.” Ibid.

can confidently say to people that it's good to exercise, how much, we'll see, it probably has the best evidence behind it. We can say to people it's good to remain cognitively engaged, it's good to remain socially engaged, it's good to remain active, but I don't think we're at the point where we can give people a specific recipe. That gets a little misleading.

But it's the zeitgeist now. ...Anyone you talk to, I'd say, above 55, above 50, probably, they're all, oh, I do crossword puzzles – they've all accepted it already that engaging in cognitively stimulating activities will help them...over the last few years there's just sort of become taken for granted that that's really true. And, you know, there's all these truisms, people go out there, well, really what's better is to do something you never did before, that's better than doing what you always do....or learn to juggle, or, you know, learn a new language. All of these things sort of sound good, but the evidence is really not there.

.... It's translating [the epidemiological evidence] into practice that's hard, more than just saying basically what I feel comfortable saying: It's good to exercise, it's good to remain active, it's good to be socially engaged.... Based on what we know from epidemiology. But I can't tell you oh, here's what's enough....[I can't say] [t]he dose, and I can't predict really the response. In general, we know it's good.

...I think in the end you need randomized trials. You know, you wouldn't accept any medication without them. That's sort of what we're talking about here. I think the problem is that it's easy to say that. They're very hard to design.... [I]t's very hard to define your outcomes in a meaningful way. Maybe some people are doing a better job than I am, but just looking at like cognitive testing, or neuropsych testing (pre/post), I don't think that's sufficient. And it's just hard when people are healthy, I think it's hard to effectively measure how well they're functioning. When someone has Alzheimer's it's easy to show that they have deficits in Activities of Daily Living or even early on Instrumental Activities of Daily Living, but in healthy aging we're talking about very different, subtle things. Not that the person can't drive, maybe they don't drive to unfamiliar places, you know, or maybe they don't drive at night, they're very subtle and they're very individualized and so I'm worried that we don't have optimal outcome measures.

In the long term if you do very long term studies over several years, you could look at reducing the rate of cognitive decline, showing differential rates of cognitive decline. I think that would be compelling, but you know you need 45 years to do a study like that. It's very expensive. But you know like we did this study where we had people playing this very complex video game. They came in three times a week for 12 weeks –The Space Fortress.

So they played it 36 times. It's a complicated game, and they have to coordinate a lot of stuff. We had very strong theoretical reasons for how we did it, and the kind of training that we used, and all of that, and in the end on my pre/post battery I showed that people who played the game learning it the way that I felt was most efficacious did a little better on some working memory task. But my colleague, who's a human factors guy, said, what kind of measure is that? You had them mastering this very demanding game that helped them improve their attentional allocation and their coordination of complex activities and goal setting, it's probably affecting their lives in ways that you don't even know how to capture....But, you know, I'm a neuropsychologist and in Alzheimer's trials it was easy, you could use a mental status test and it was good enough.

... I still think there's a positive message there, and I do believe that it's true, but like I say I think more work needs to be done if you want to specify to people. I think it's fair to say that people who are more active, more socially engaged, more physically active, do better. We see it in study after study after study.... I think that it makes a difference....I really think it makes a difference.... but it's a very nuanced message.<sup>7</sup> You know, like I had a TV news station come to me and they told me that they wanted me to go around and give people crossword puzzles and tell them that if they do that every day, they'd age more successfully. I said, "You know, I can't say that." But people will. People do. So you just got to be careful about what you say.

I'm interested in cognitive reserve, I think it's a very hopeful message. I'm trying to understand how it works, what it is, and, you know, truthfully my stance for a long time was it was not time for me to do intervention studies because I don't understand the neural substrate of how reserve might work well enough to focus my intervention. But I've come around to the idea that you can take what you think is probably right and try it and understand that part of it.... like the simplest idea, like I used to say, when my daughter was learning seven plus six and having a hard time remembering thirteen, I said oh, do seven plus three plus three, that's how I do it, I do it by tens, right? A lot of us do that with math, we adapt our approach, you know we do things by fives, by tens, so I said that could be sort of like what reserve is,

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<sup>7</sup> Yaakov Stern, interview by author, New York, NY, October 10, 2011. The full exchange was as follows: YS: *I think it's fair to say that people who are more active, more socially engaged, more physically active, do better. We see it in study after study.* AV: *Do better or are better?* YS: *Do better cognitively. Do better over time.* AV: *But does it just mean that they're already better?* YS: *No, I think that it makes a difference.* AV: *Ok.* YS: *I really think it makes a difference.* AV: *So that could be a message?* YS: *Yeah. But it's a very nuanced message.* I was probing Stern's potential message for his views on causality between life-style behaviors and cognitive health. From surrounding context I interpreted "nuanced" as meaning general.

that you have multiple ways of attacking a problem, but to show that with imaging is very very difficult. You could do that experimentally. So we're working on different approaches to that.<sup>8</sup>

In the above passage Stern suggests the claim that *We can recommend cognitive engagement, social engagement, and physical engagement in general terms for cognitive health*. It sounds like a general prescription for good living but it is nevertheless a statement in the service of cognitive health that has not been endorsed officially to date. Stern offers no specifics, such as particular cognitive activity (crosswords puzzles being the quintessential example) or strategies (such as doing something you've never done before). He cannot even specify any particular exercise dose ("how much, we'll see"). It further sounds like he cannot even specify whether cognitive or social or exercise in isolation that would be effective. This can be inferred because he does not seem to endorse a message that "engaging in cognitively stimulating activities will help" but instead repeats the combination of behaviors as a composite. This is the most general message offered by any of the interviewees. But he does insist multiple times that it can be said.

The evidence that Stern points to many times is "compelling" epidemiological evidence and perhaps also available trials linking behavior with cognitive health in support of a general message ("We see it in study after study"). However, "in the end you need randomized controlled trials" to offer a specific "recipe/prescription," that is, "if you want to specify," which is ideal. Stern mentioned ACTIVE as one of the first RCTs on lifestyle issues but did not endorse

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<sup>8</sup> Ibid.

its findings. He and colleagues wrote elsewhere that “the lack of a significant general improvement in all domains of cognition suggests that the key to promoting cognitive flexibility may lie elsewhere. For example, it may be that training that promotes the use of flexible strategies for solving novel problems may confer the most benefits for cognition and function.”<sup>9</sup>

Any more specific conclusions than Stern’s general message will depend on the working out of measurements, especially establishing the outcomes that we are looking for. While Stern throws out some suggestions for outcomes (avoidance behavior such as avoiding driving to unfamiliar places, avoiding driving at night), he also makes clear that you could look at many behavioral realms and that outcomes have not yet been worked out. Further, Stern pointed to the need to develop meaningful outcome measures that are functional in nature. We need to look at how these activities are “affecting ... lives” instead of using a “pre-post battery” of lab-based attention tests and goal setting (indications of executive function). He implicates himself in this study limitation and suggests that the shift to healthy aging from disease prevention represents a kind of paradigm shift that researchers are perhaps not quite ready to tackle. He explains later that he is currently studying cognitive reserve by comparing imaging with activities and behavior to see how different levels of activity moderate pathology, even opening up the possibility that pathology might not only be compensated for or circumvented but might even be lessened by the activity.

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<sup>9</sup> Adam M. Brickman, Karen L. Siedlecki, and Yaakov Stern, “Cognitive and Brain Reserve,” in ed. Colin A. Depp and Dilip V. Jeste, *Successful Cognitive and Emotional Aging* (Washington, DC: American Psychiatric Publishing, Inc., 2010): 157-172.

The warrant for Stern's *Epidemiologically Informed Policy Argument* is that compelling epidemiology along with the trials that have been done are enough to issue general recommendations for cognitive health at this point in time. General recommendations are something that have not been offered before and so do represent a real message of sorts. Stern implies that the backing for his warrant is that there would be no danger in issuing recommendation of healthy living for brain health: "In general we know it's good."

Stern's backing for his warrant is that we know the ingredients (physical, social, and cognitive engagement) even if we can't recommend specific recipes. It is a message a bit like the USDA's ChooseMyPlate program (ChooseMyPlate.gov) which that about half of one's diet be comprised of fruits and vegetables, without explaining which proportion of which particular fruits or vegetables or without advocating a specific form of preparation.

Stern's discussion of the difficulty of defining healthy cognitive outcomes raises a major research barrier to the promotion of cognitive health. The State-of-the-Science Conference Statement acknowledged this problem in negative form: "Some of the main reasons for the inability to identify successful interventions may include (1) lack of a validated and consistent definition of cognitive decline...."<sup>10</sup> The issue of outcomes took up a large portion of my interviews but extends beyond of the scope of the current project. There was near unanimous agreement that outcomes should be functional rather than based on

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<sup>10</sup> Martha L. Daviglus et al., "National Institutes of Health State-of-the-Science Conference Statement: Preventing Alzheimer's Disease and Cognitive Decline."

biomarkers alone. In other words, the ability to function in everyday life mattered more than the presence of Alzheimer plaques and tangles in the brain.<sup>11</sup>

### **Control of Hypertension and Physical Activity for Cognitive Health**

Two researchers interviewed delved into the vascular-cognitive connection, Peter Rabins of Johns Hopkins University and Peter Whitehouse of Case Western University, using different arguments for public health action. I will quote a passage from each interview, analyzing each in turn, beginning with the words of Dr. Rabins. Dr. Rabins presents the view of a practicing physician who has treated Alzheimer's disease for most of his career and who was asked to serve on the advisory board at the Alzheimer's Association and later on the Healthy Brain Initiative (Prevention Research Workgroup).

#### Peter Rabins

[T]he idea that primary prevention might really be the most effective strategy, in a sense, for wiping out the disease seems like an obvious point for any of us, but it hasn't really been a major focus, I don't think, of people that are studying Alzheimer's disease and dementia and thinking about the treatment, if you will, so I think part of the timing [of the HBI]

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<sup>11</sup> How did these researchers define a healthy brain? They described it in terms of what it enabled an individual to do and what benefits those functions conferred to society. To Dr. Jennifer Manly it is a brain that can "learn," "be flexible," "produce," and "control your body in the way that it needs to." It is also one that is "thriving" at any age. Healthy elder brains are valuable to society because they yield "stored wisdom and stored knowledge." To Dr. George Rebok a healthy brain keeps us "engaged," "connected," and "functioning" in society, and it builds societal engagement, civic engagement, and social capital among social groups. To Dr. Stern the healthy brain "is able to maintain function." To Dr. Whitehouse it enables "learning," "action," "creativity," and "adaptability." Dr. Whitehouse summed up the general view of the interviewees by saying that a healthy brain is "a brain that acts in the world." The two geriatric psychiatrists offered definitions that included emotional qualities. In defining the healthy brain, Rabins mentioned "cognition," "behavior," and "emotions." Dr. Hugh Hendrie pointed to three integral functions: "cognition," "emotion," and "motivation." Dr. Leonard Poon noted that the "Brain is physiology but cognition is more than physiology – it encompasses physiology and sociology and psychology." He further called cognition "a behavioral output," or function. Many of the researchers emphasized the difference between structure and function as crucial to the understanding of cognitive health.



was that there was sort of frustration with the treatments that were available, and although there was optimism that some of the new directions that were being taken in therapeutics might really make a difference, again I do think people were starting to realize that those therapies might only slow the disease down or might stop it in its tracks but not allow for recovery, so again I think as people thought about the implications of that again it turned people's thoughts toward primary prevention. I do think that was one of the underlying themes.

[M]y view is that even though the CDC has been turning in the direction of chronic illness prevention and care for a long time, there's been very little focus or realization that dementia is really a huge public health issue within the chronic disease field. And I think there was kind of a lack of recognition that the vast majority of people in nursing homes, for example, are there because of dementia, that this is a *huge* expense, if you just look at the economics, that this is a tremendous part of both state and federal budgets, so the public health issue isn't just the fact there are 4 or 5 million people who have these diseases, and 10 million caregivers that are providing informal or formal care (that may not be the right number), but from a health expense point of view it's a huge issue, and I think for whatever reason the public health field has been very slow to appreciate that.

...So that's why I see the interest in brain health as sort of the positive way of thinking about dementia and brain aging....I think there was sort of an underlying hope or assumption that ... if we could figure out how to maintain a healthy brain that that would lead to strategies to prevent the diseases that cause cognitive decline, dementia. As far as I'm concerned there's no evidence that that's true, but I do think that was an assumption and still is an assumption that we made.

...There was an NIH Consensus Conference, whenever it was, a year and a half ago now, that I was not in any way involved in. That took a very hard-nosed scientific literature review approach to the question of whether we can at least prevent dementia... My sense is that that was a very negative. Well, first they didn't find good evidence that anything can be done to at least prevent dementia, that's sort of my bottom line, which I partly agree with, or at least which I do agree with at the level of clear and convincing evidence. I think where they missed the boat, is the idea that, first that there's not a clear recognition in the report of how difficult it is to do primary prevention studies of the prevalent chronic diseases. We can look at preventing single events like strokes and heart attacks or death, those kinds of hard outcomes, but performing studies to demonstrate that you can lower rates of heart failure or diabetes or depression or dementia is a very different magnitude of study. Because you require very

large groups of “healthy normal people” because the incident rate of your outcome is relatively low, you have to follow them for long periods of time, and I don’t think there’s an appreciation in that report that we don’t have that evidence for *anything*. I do think there should have been more emphasis on epidemiologic findings, for example, that midlife hypertension is correlated with the development of dementia in late life, and that if you were going to study that it would take 30 or 40 years and I’m not sure that that kind of study can or should ever be done. What, we’re not going to treat people with hypertension? Right? I mean, it’s not possible. Or if you’re interested in exercise, so are you going to tell people they can’t exercise? You can’t do crossword puzzles? Or you can’t be socially engaged? I think, at least what I saw in the report, there wasn’t a recognition that those kinds of primary prevention studies will be very difficult to do, not just with dementia but with a lot of the common disorders.

So, again, to me personally, the most convincing evidence now is that early and adequate treatment of hypertension and diabetes in midlife, and probably other vascular disease risk factors, is likely to have some primary and maybe secondary preventive effect. I just don’t think that was one that was highlighted. And then number 2, that since the effectiveness of those approaches in preventing heart attack, stroke, death and the complications of diabetes, that they are well established, that it’s a very low-cost intervention and so, I think, to be totally hard nosed and say, you have to have clear and convincing randomized trials – I think that’s the wrong standard.<sup>12</sup>

In this passage Rabins narrates a kind of flip from the cure-based perspective of medicine to the health-maintenance perspective of health promotion. He uses the term “primary prevention” to signify the effort to prevent risk factors from developing. He describes drug limitations and trial failures as the turning point in the narrative, which represents a move away from a pharmaceutically based solution towards an openness to other possibilities for health promotion.

Rabins represents the health promotion argument as a false argument. The claim is that maintaining a healthy brain will prevent disease. The claim is

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<sup>12</sup> Peter Rabins, interview by author, Baltimore, MD, August 11, 2011.

merely an assumption, which may or may not be true, because there is no evidence to back it up. How can it be warranted? Only through wishful thinking and this warrant cannot be backed. One might say that there is no harm to this wishful thinking, but that is arguable because it reduces credibility of the organizations issuing the recommendations.

Finally, Dr. Rabins implies that an argument can and should be built around evidence we do have for public health action. Its claim is that *We should control hypertension and diabetes in midlife to protect the brain*. Rabins asserts that “the most convincing evidence” for prevention is epidemiological data that treatment of hypertension and diabetes in midlife lowers incidence of dementia in late life. This evidence only works with the warrant that epidemiological data can be used in lieu of RCTs, a very different warrant than the one used by the State-of-the-Science Conference. Indeed he insists that the kind of RCTs that we would need cannot ethically be done. It is a warrant backed by the particular context of the times, which Rabins depicts as a sort of public health crisis. Dementia is a huge public health issue within the chronic disease field. Most people in nursing homes have dementia. Rabins alludes to the public Medicaid expense of paying for institutionalizations (Medicare doesn’t cover long term care so it reverts to public assistance, a joint federal and state program). Yet he notes that patients are not the only ones afflicted, caregivers too are involved in the suffering, sacrifice, and financial expense of this issue. The warrant is backed by a moral imperative to do something amid the suffering.

In short, the stakes are too high to use the highest standard of evidence. Rabins turns the tables a bit to suggest an inability for medicine to cope, the

slowness of public health to get involved, and the abdication of responsibility on the part of the State-of-the-Science Statement because of its epistemological stance because he agrees that the RCT evidence is not available for preventive interventions. Imagining attempting to conform to the Panel's requirements of multiple large RCTs confirming results on this complex topic, he notes that no chronic disease research has been able to meet these demands to date. He alludes to the prohibitive costs of the required research because of the huge numbers of participants needed. More importantly, however, the needed studies would not be ethical. RCTs require a control group that does not engage in the intervention being studied, and prohibiting people from engaging in potentially healthful behaviors for 30-40 years would be absurd. In the absence of the ability to fund or do the kind of research they are asking for, the Panel should at the very least have noted the very low cost intervention that has been shown to avert cardiovascular disease and add a cognitive health message onto it. In my view, Dr. Rabins is a strong proponent of *Epidemiologically Informed Policy Argument*.<sup>13</sup> However, his policy seems to apply at the level of secondary rather than primary prevention.

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<sup>13</sup> Hendrie also was troubled by but also ambivalent about the strict reliance on RCTs at the State-of-the-Science Conference: In an interview on September 15, 2011, he stated that "There was a problem in that they [NIH] weren't content with longitudinal/observational studies – the evidence wasn't conclusive unless you could turn it into randomized clinical trials. That was the message. Mostly they were right. But some of the clinical trials would have to start at age 40-50 and be conducted for 30 years. The Women's Health Study did that, so there is precedent." See also Marcelle Morrison-Bogorad, Vicky Cahan, and Molly V. Wagster "Brain Health Interventions: The Need for Further Research," *Alzheimer's & Dementia* 3, no S2 (2007):S80-S85, two participants in the HBI from the National Institute on Aging and a colleague referred to the Women's Health Study as an RCT that demonstrated how animal findings can mislead researchers in their application to humans: "Animal studies do not prove the same changes take place in the human brain with a particular level of exercise, and the human observational studies cannot definitely separate the effects of an active lifestyle on maintenance of cognitive health from other healthy behaviors. Such limitations have become startlingly clear with recent reports from

Dr. Peter Whitehouse seems to argue for a similar claim as Dr. Peter Rabins while using a different warrant. Below is a passage on cardiovascular risk factors and dementia pulled from my interview with him:

Peter Whitehouse

...[T]he Alzheimer's model is failing. We've had years and years of promises about drugs to fix Alzheimer's. And now people are starting to realize that perhaps the pharmaceutical model will not work, and if you do take a broader look at Alzheimer's, as we tried to do in *The Myth of Alzheimer's* and say this [Alzheimer's disease] is not one thing, it is related to aging, more and more epidemiological research suggests that you can prevent Alzheimer's, i.e., improve brain health, by lifestyle issues....[T]he brain is very salient, that's why it's a good point of leverage, and it's very salient in part because as the baby boomers age they're well aware of their own mental changes and they also have the fear of Alzheimer's....

...[T]he consensus panel on preventing Alzheimer's and cognitive decline ... concluded that the evidence was *not* conclusive enough to warrant recommending people change their behavior. I think that was a very unhelpful conference because I think you've got to rethink the epistemology of how you take action in the world....We have created this sense, and this panel reflected it, that you've got to have randomized controlled studies to demonstrate the value of everything. And I sometimes refer to randomized controlled studies as the gold standard because only people who have gold can afford to do the studies. And that's really true. The pharmaceutical industry can afford the tens of millions of dollars to do relatively simple interventions on taking one of two pills, you know, a placebo or not a placebo. If you start talking about doing research on an intervention like our Intergenerational School, it becomes enormously more complicated to do, enormously more interesting ethically wise, enormously more problematic in terms of interpretation of results. So you almost set up a system where pills are the only answer because they're the only ones you can do randomized controlled studies on.... What I'm saying is, when I said they need a broader epistemology, is they need[ed] to consider different evidence.

...They say that 80% of medical practice doesn't have an evidence base, if you're considering it as randomized controlled studies. Particularly in aging, it's practically impossible because

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clinical trials of menopausal hormonal therapy, in which findings from animal and observational studies were not borne out for particular groups of woman."

in a randomized controlled study you have people in the study who only meet certain criteria, like they're very healthy, they're NIH super volunteers. So when you get to being concerned about generalizability, for example, and generalizing into a patient population that wasn't in the study, most older people can't because they have multiple co-factors – I mean, randomized controlled studies are in some sense very limited in the sense that they really, epistemologically if you think about it, only pertain to the people who are in the study. I mean it's even difficult to generalize outside from people in the study. So I think we have to consider epidemiological information, and they should have considered that more, I think they have to be a little less FDA-like in evaluating studies, I think they have to consider even narrative. Now narrative is to me very powerful, the stories that people tell about their health. I realize that anecdotes are one-person stories, but if you take a bunch of stories and put them together you can analyze stories as a kind of collective narrative and that becomes a more powerful body of evidence. So I'm just saying we have to be smarter about what we constitute as evidence. As far as I know, they did a very comprehensive review of the literature, I wouldn't fault them on that.

... Physicians are very biased by, like, the last case that they saw. Randomized controlled studies are biased by whoever is going to be recruited into randomized controlled studies, which is a pretty weird bunch of people, frankly (no offense to them). And epidemiologists can be biased based on what sample they have in their study. So, in many ways, the best study you could generalize from is a randomized, stratified sample of the entire human race, if you want to generalize to all of mankind. That's not possible. But you still have to be aware of your recruitment biases, you know, regardless of what you – the limitations of the study are important.

...It would be very interesting to know, if they [another NIH state-of-the-science panel] picked a randomized controlled trial, you know, do the same thing, for cardiovascular health, whether it would come out the same way. Probably there's more evidence, you know, for things like exercise and other things, but given that if you improve heart health you improve brain health, and people that have heart attacks and congestive heart failure clearly have problems with issues having to do with cognition, if you considered cognitive decline and you considered ok we want to prevent people who have heart attacks and who have brain damage or people who have congestive heart failure you could probably have found enough evidence for that and then said with regards to cognitive decline, it would be worth a public health campaign.... This may be a case where you don't need evidence. Since the heart pumps blood to the brain, if you don't have a heart

that's working well, you will have a brain that doesn't work well. That could be in two situations that I imagine. One is if the heart stops and you have toxic brain damage on a temporary basis. The other is if you have congestive heart failure and periodically your brain stops being perfused adequately....[interruption]

...if you google the "myth of Alzheimer's," it comes up as the myth is that, you know, that memory loss is inevitable with aging. Well, it is, to one degree or another, and you can never do the experiment of if we all live long enough, would everybody get it? But basically the frequency of incidence of dementia even, let alone mild memory problems, goes up increasingly with age. So I think this was part of the fantasy world that if we cured Alzheimer's disease somehow we'd all live with perfect memories. Nobody ever asked the question, Ok, if we find the cure to Alzheimer's disease, what is brain aging going to look like with Alzheimer's cured? Are we going to age with the rest of our bodies aging and our memories not? It's so actually logically inconsistent it's hard to know why people have managed to make this argument successfully. But yes, I believe that basically Alzheimer's is one of several forms of severe cognitive decline, people whose brains unfortunately have aged faster than the rest of them. I'm of that ilk.<sup>14</sup>

Similar to Rabins, Whitehouse first exposes a false argument. He critiques the State-of-the-Science Conference for claiming that *People should not at this point change their behavior for cognitive health*. The evidence given is that no evidence is conclusive enough to prove that changing behavior prevents AD or cognitive decline. The warrant is a conventional and widely accepted one in the science world, that we need RCTs to be conclusive. The backing for this standard, the warrant, is that it is the pharmaceutical standard that we have agreed on for treatment recommendations.<sup>15</sup>

Like Rabins, Whitehouse has no fault with the evidence for the Panel's claim, as he praises the Conference for a fine review of the literature. Instead he

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<sup>14</sup> Peter Whitehouse, interview by author, telephone, September 19, 2011.

<sup>15</sup> In support of this backing, I will re-quote Yaakov Stern, interview by author, New York, NY, October 10, 2011, about the lifestyle modifications examined by the State-of-the-Science Conference: "I think in the end you need randomized trials. You know, you wouldn't accept any medication without them. That's sort of what we're talking about here."

challenges the warrant that RCTs constitute the only form of evidence on which policy (i.e., action) can be built. Changing the warrant would change the evidence and lead to a different conclusion. Whitehouse objects to the warrant on several counts. He challenges the integrity of RCT evidence as it applies to the aging population. He sees conflict between the demands of the standard (that subjects be free of any problems except for the issue under examination) and the population the intervention is intended to reach. Since the vast majority of elders have comorbid conditions, the insistence that the study pool be free of conditions creates a pool of “NIH super volunteers” that represents no one.<sup>16</sup> In fact, Whitehouse implies that RCTs do not even meet their own standards of generalizability because that would have to involve “a randomized, stratified sample of the entire human race,” which is absurd.

Second, Whitehouse raises the possibility of a double standard, asking whether cognition is treated differently from cardiovascular health. It is interesting that an objective for the NIH’s 1996 Conference on Physical Activity and Cardiovascular Health was to provide physicians and the general public “with a responsible assessment of the relationship between physical activity and cardiovascular health.” The goal was not stated as definitive proof. In addition the statement summarizes the evidence in ways that suggest a majority judgment, as when it says “Most [not *all*] studies of endurance exercise training of

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<sup>16</sup> Hugh Hendrie, interview by author, telephone, September 15, 2011, described two forms of clinical trials. The first is what we usually talk about, testing an intervention on a select group of people. The second is an effectiveness trial that translates the trial into a clinic-based population, and “these are seldom done.” Effectiveness trials take 10-20 years and uncover a wide set of side effects on many different kinds of people but confirm that they are not enough to avoid prescribing the drug to most patients. We might add here that in public health the translation would occur at a community-based level, and it is with this diverse patient pool that “you get all the side effects.” Clinicians “need to be able to prescribe to any patient.”



individuals with normal blood pressure and those with hypertension have shown decreases with systolic and diastolic blood pressure.”<sup>17</sup>

Third, Whitehouse argues that other kinds of evidence should not be ruled out because they are more complex than the drug model. Other promising interventions cannot be realistically measured with clinical trials. He mentions his Intergenerational School, an intervention that combines cognitive engagement, social interaction, community engagement, and presumably physical activity for the cognitive health of older adults. Alternative kinds of evidence he would include are epidemiology and narrative.

After critiquing the State-of-the-Science Conference Statement claim that there are no recommendations for the public for cognitive health, Whitehouse offers a similar claim to Dr. Rabins’s but in more general form. His implicit claim is, *We should recommend heart healthy behaviors to protect the brain*. The evidence for this claim is that an ineffective heart pumping action directly affects cognition. Whitehouse provides two examples of ineffective heart pumping. In the first case (“if the heart stops and you have toxic brain damage on a temporary basis”) he seems to be referring to an arrhythmia (as in atrial fibrillation), which is damaging on its own but can be the major precipitating factor for stroke, which invariably results in brain damage. In the second case (“if you have congestive heart failure and periodically your brain stops being perfused adequately”), the heart muscle would be enlarged and weakened. Because of this direct effect, behaviors that promote blood perfusion or prevent heart stoppages

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<sup>17</sup> Luepker et al., “NIH Consensus Development Panel on Physical Activity and Cardiovascular Health.”

would protect the brain, as backed by the examples of stroke, heart arrhythmia, and heart failure. Although Whitehouse does endorse the use of a combination of evidence to make responsible recommendations, thereby recommending triangulation across the evidence (a *Triangulated Evidence Policy Argument*), I think most forcefully he argues for a warrant of common sense (“This may be a case where you don’t need evidence”) because of the direct physiological effects of heart pumping action on oxygen to the brain. He therefore offers an example of the *Logically Derived Policy Argument*.

Like Rabins, Whitehouse further supports his argument that vascular evidence can be used as cognitive health evidence with the suggestion that we are in a kind of public health crisis. As Whitehouse sees all forms of dementia as connected to aging, he expects rates to increase at the same time that other planetary crises require the collective wisdom of intact elder brains. Later in the same interview he states that:

the fact that if individual members had healthier brains then the collective wisdom (a word I use not infrequently) of the community would be better. And that I use to say that that’s a very important issue, because our civilization is totally threatened and our species is threatened because we are *not* operating with enough collective wisdom to address social and environmental challenges. So it means a *lot* to the community to have individual and collective healthy brains.

To Whitehouse cognitive health is a population-level issue because of large-scale global issues that require a combination of age-related experience (wisdom) and brain power to solve.

Dr. Whitehouse offers an example of the *Logically Derived Policy Argument* by suggesting that vascular evidence can in a sense be co-opted in the

service of cognitive health promotion. Although his claim is similar to that of Dr. Rabin's the two use evidence differently. Dr. Rabins would widen allowable evidence to include longitudinal studies, whereas Dr. Whitehouse would logically graft vascular evidence to cognitive outcomes. The gist of his argument is that we can promote heart healthy behavior for cognitive health because heart health directly affects brain health.

### **An Argument for Physical Exercise**

Neuropsychologist Jennifer Manly of Columbia University used Art Kramer's model of research to endorse physical exercise for brain health. She did not specify that its benefit was due to vascular factors but mentioned a range of possibilities. An excerpt from her interview follows:

#### Jennifer Manly

[T]here are some things that clearly, I think, are promising. You know, aerobic exercise is one of those things. I think that we have some darn good evidence in randomized trial studies that exercise can help a whole myriad of things, and it's not exactly clear the mechanism, I think, but it can maintain healthy cognitive function. It may be through mood, which is another thing that it seems to have an affect on, but it may actually be through increased, healthier vasculature of the brain, it may be through new cell generation, you know, who knows what the mechanism is. People are working hard on that. But I do think that's probably the only thing I've seen out there, the only intervention that's been properly tested [with randomized controlled trials] that seems to make a difference.

The issue there is that you want to be able to tell people that this makes a difference over and above whatever other things drove people to exercise in the first place. So what we have, ok, let's say we find out blueberries. Ok, we have an observational study, we ask everyone exactly what they eat all the time every day and then we find through our statistical analyses that the people who eat more blueberries have healthier, better cognition. They

could have better cognition at that time point when they're eating blueberries, they could also have better cognition later on when we visit them five years later, they could maintain their cognitive function while everybody else is going down. So then I write a study, blueberries are healthy for the brain. The problem is it's possible that a whole different kind of person eats blueberries. Like who would eat blueberries? You go to the store, they're super expensive, when they're not in season they taste funky, maybe they're all from California, these people, who knows, I'm just making up stuff. Different kinds of people eat blueberries. Maybe some other factor – maybe these people are better off. Blueberries are \$5.99 a packet. Yeah, they're tasty but you can only afford them if you have money to spend. And that money could also go to access to healthcare, it could also go to a gym membership.

...What I'm saying is that there's a lot of messiness in what we measure. And so the best way to do it is a randomized trial, where you take a whole bunch of people, they are the same essentially on average to begin with, and you put one group randomly (roll the dice or flip a coin) and you put one group into the treatment trial and you put another group into a trial where they're getting everything that the other folks are getting except for the actual thing. So in drug trials they do it with a placebo, in exercise trials they get them together socially because that's what generally happens with exercise, you do it in a gym or you do it on a treadmill or something, but they do something that's not aerobic, so they'll do stretching or like yoga or something. So the difference between those two groups, theoretically, the only thing, is that they're getting the aerobic. It's hard to do in a lifestyle intervention, though.

[On evidence right now to promote behavior change:]  
 What I think we have, as I said, we have exercise. We have one thing that I would put everything behind.... What I would say is, of course, consult with your doctor, because not everyone should go out and do aerobic exercise, but I *would* say to people who are in their thirties, forties, fifties, that, you know, exercise is very important to keep your whole body healthy including your brain, and to figure out a way to get that done for yourself now is going to help you later in life to continue to do it better in life. Form a routine that makes you feel good. Because it does feel good. It makes you feel good and that you'll want to continue. Maybe you, like I did, you know, last year, maybe you hurt your knee and you need to go do something different for a little while, but the whole idea of getting aerobic exercise is still with you, you don't lose that. Really we should be doing that. We are, but we really should be pushing with kids, because that, I think, is where it starts. And then teaching people to maintain that as their body changes over

time, you know, is really important. I was at this thing in Detroit. They have a Minority Resource Center for Aging Research out there, and they focus on African Americans....It's in Detroit, it's a partnership between two guys are the PIs, James Jackson who's at the University of Michigan and Peter Lichtenberg who's at Wayne State University. And they did this great thing. There's an African American museum, history museum, there in Detroit, and they invited the community there, and they had this guy who's doing chair exercises, so everyone was sitting down and he was up on the stage and his helpers, you know, it's like an aerobics video but it's all from the chair, so people who feel that they have limited mobility, like I can't get up, I can't move, I can't exercise because my legs aren't working, he was showing them how to do heart rate exercises from the chair that were safe and healthy, and I thought it was great. We need to teach people ways of maintaining their active, doing whatever it takes, whatever this effect is, maintaining this effect in many different ways that accommodate the aging body. So I think that would be, just focused in and of itself, would be fantastic....

...One thing I sort of said under my breath just now is that the ACTIVE trial wasn't really, that I hadn't seen evidence from the ACTIVE Trial that would make me think that there is, that that approach is one that has hope in preventing cognitive decline or in preventing Alzheimer's disease. Or in promoting or maintaining health, that that specific approach. Because the evidence is just not there. The evidence, based on the ACTIVE Trial, I think, was that there was *no* real improvement, and "real" being defined as a group of people on the basis of their experience in the trial are significantly better off cognitively than they would be had they never taken part in a trial. Had they never taken part in those exercises. I actually think that, I could be wrong. Most neuropsychologists do think that those kinds of cognitive activities could have the potential of maintaining healthy brain function, and I'm just waiting for there to be convincing evidence of that.<sup>18</sup>

Manly's claim is that *We can recommend aerobic exercise to promote cognitive health*. She makes it clear that whether it is through heart health, psychological health, or neurogenesis, exercise has been shown to "make a difference." She tempers the message by saying that people should consult with their physicians if they have health conditions before undergoing an exercise

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<sup>18</sup> Jennifer Manly, interview by author, New York, NY, October 11, 2011.

routine. She even gives the health promotional message that one should note how good it feels in order to motivate oneself to continue to establish the habit so that it will be sustainable. The habit of exercise works in different ways at different times of life, she implies, and it is good to establish the routine as early in life as possible. One established it can be adapted to the changing body even to the point of getting aerobic exercise through upper torso movements if one can no longer walk.

Manly states elsewhere in the interview that the evidence for her claim are RCTs specifically conducted by Art Kramer's lab. Those studies randomize people so that they are presumably unaware of their intervention condition (aerobic vs. toning) and then measure pre- and post- change on measures of cognition. In contrast, she gives an example of an RCT (ACTIVE) that does not seem to make a difference. According to Manly, the effect sizes are not large enough or meaningful enough to warrant a recommendation for cognitive engagement to promote cognitive health.

The warrant that Kramer's work proves that we should be exercising for brain health is that they are RCTs that represent the highest standard of evidence. Manly backs the warrant with a thorough explanation of why RCTS sort out the behaviors that do or do not "make a difference." Her hypothetical example displays the weakness of observational studies, the mainstay of epidemiology. Even if a correlation is found between eating blueberries and high cognition at a later point in life, one does not know if it is the blueberries or another factor that contributed to the difference. However, epidemiologists do typically "control" for

various factors such as income to try and isolate the behavioral variables that are significant.

Thus, Manly makes an *Evidence-Based Policy Argument* that physical activity can be promoted for cognitive health. In this she stands apart from the verdict of the State-of-the-Science Conference statement which, in fact, fell short of endorsing exercise as a behavior, while at the same time endorsing the statement as “very accurate.”

A focus on the arguments in favor of cognitive health messages has revealed examples of the *Evidence-based Policy Argument* (Leonard Poon, Jennifer Manly), the *Epidemiologically Informed Policy Argument* (Peter Rabins, Yaakov Stern), the *Logically Derived Policy Argument* (Peter Whitehouse) and the *Triangulated Evidence Policy Argument* (George Rebok). All of the researchers with the exception of Poon suggested that public health messages could be issued to promote cognitive health on one or another dimension. The messages ranged from the very general (Stern’s *Exercise, remain active, be socially engaged*) to the more specific (Rabin’s *Control hypertension and diabetes in midlife*). The researchers differed greatly in the degree to which they were willing to cross out of their disciplines into a public health policy realm. Poon did not go there, and he and Manly adhered to the strict standard of RCTs. The other researchers justified their use of additional forms of evidence with warrants that noted the limitations of RCTs and were backed by a moral imperative of public health urgency amid population aging that called for a different set of standards.

From my viewpoint, the *Logically Derived Policy Argument* makes the most sense because it uses proven interventions and existing public health

messages to address a secondary outcome of cognitive health. Rather than waiting to redo trials for cognitive health, which may never be feasible, existing trials can be interpreted in the service of cognitive health. Interventions that are familiar to the public but are underused (i.e., physical activity) are promoted with an additional benefit. The risk of issuing a wrong message in this case is a healthier population.



## Chapter 5

### Discussion

This qualitative research project has addressed the question *Why have no public health recommendations been issued nationally for older Americans to maintain or promote their cognitive health?* and the deeper questions *What is adequate evidence for issuing public health recommendations?* or *When do we know enough to act?* Interviewee discourse examined with the Toulmin model of argument analysis suggested a number of arguments that can be used to make public health recommendations for cognitive functioning in aging. These ranged in order of specificity based on the warranted evidence used. On one end of the spectrum was Stern's very general recommendation that cognitive, social, and physical engagement (in some combination) could be recommended to promote cognitive health, using an *Epidemiologically Informed Policy Argument*. On the other end was Rabin's specific recommendation for midlife control of hypertension, also using an *Epidemiologically Informed Policy Argument*. In the middle were recommendations for preventive heart health behaviors (such as low-fat diet and physical activity) for cognitive health. Whitehouse also recommended heart healthy behaviors but with the more powerful *Logically Derived Policy Argument*. Rebok recommended cognitive engagement based on a *Triangulated Evidence Argument*.<sup>1</sup> Manly recommended physical exercise using for cognitive health using the black-box paradigm and an *Evidence-Based Policy Argument*. Poon, like the State-of-the-Science Conference Statement, did

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<sup>1</sup> Peter Whitehouse also supported combination evidence, but as they offered the stronger *Logically Derived Policy Argument* I represent him with this argument type.

not endorse behaviors for cognitive health using the *Evidence-Based Policy Argument*. Are any of these arguments strong enough to justify a public health agenda? I believe so.

The *Evidence-Based Policy Argument* lives and dies by the strength of supporting RCTs. Using an *Evidence-Based Policy Argument* alone, I do not think we could not proceed with a public health agenda at this time. While the cognitive fitness marketers have claimed that cognitive fitness works based on the ACTIVE and/or IMPACT Trials, researchers including Poon and Manly have questioned the impact of those trials based on small effect sizes and not accounting for individual performance variability because of reported participant averages. My own reading of these trials as presented in Chapter 2 found that vague explanation of performance scoring and conflicts of interest further cast doubt on the claimed findings. However, other aspects of these trials, such as the training effects, are impressive and could be strengthened with further evidence.

The *Epidemiologically Informed Policy Argument* has been too weak to stand up to the *Evidence-Based Policy Argument*. Under the Evidence-Based paradigm, epidemiology is preliminary evidence for RCTs, which are then definitive. The *Triangulated Evidence Policy Argument* legitimately triangulates across multiple forms of evidence to judge the cumulative weight of evidence. However, it moves too far away from the dominant paradigm to be effective at this time.

Today the *Logically Derived Policy Argument* is the best argument to further public health action for cognitive health promotion. At this point in time the vascular-cognitive behavioral link represents the easiest and least

controversial way to make an impact on population health. This approach would add a cognitive message to already existing guidelines for lowering hypertension, engaging in physical activity, maintaining weight, eating a low-fat diet, and so forth, stating that such activities are not only good for the heart but also they are good for the brain. That such an argument appears to have been missing in the national arena is unfortunate because of lost time but is also hopeful because it points to an untried path for public health. Just stating that cognition is an outcome of vascular health would importantly acknowledge cognition as an important aspect of daily life that has been too long neglected within public health. More importantly, if messages for cognitive health provide extra motivation for Americans to create heart-healthy environments or to engage personally in behaviors for heart health, the impact on public health for millions of people could be profound.

Thus, in the absence of clear RCT evidence supporting particular interventions for cognitive health, a clear and justifiable course of immediate public health action is to endorse behaviors to promote heart health because of the direct effect of cardio vasculature on cognitive health. The *Logically Derived Policy Argument* can use the “evidence-based” evidentiary standard by pointing to RCTs that have supported proven and accepted guidelines for behavioral interventions for heart health (such as the NIH Consensus Development Panel on Physical Activity and Cardiovascular Health’s guideline of 30 minutes of moderate-intensity physical activity on most days of the week for cardiovascular

health, including high blood pressure<sup>2</sup>). These same RCTs can be used to promote cognitive health with the warrant that vascular factors directly lead to cognitive outcomes. The *Logically Derived Policy Argument* makes room for common sense and logic to warrant the use of evidence accepted for one kind of problem that is a physiological pathway to another kind of problem.

A specific logically derived policy argument that can be used for public health action might be delineated as follows: As hypertension is a risk factor for cardiovascular disease and cardiovascular disease leads to vascular cognitive impairment, control of hypertension can prevent cognitive impairment. As physical activity can prevent and control hypertension,<sup>3</sup> we can recommend physical activity for cognitive health.

### Strengths and Limitations

To my knowledge this is the first study examining arguments for and against issuing policy recommendations for cognitive health in aging. The issue is of immediate and of long-ranging public health concern due to public fears about cognition, the exorbitant personal and monetary costs of caring for people with dementia, and the projections that cognitive impairment prevalence will rise with continuing population aging. The arguments by prominent cognitive health experts provocatively question whether the randomized controlled trial standard used by the State-of-the-Science Conference on Preventing Dementia and Cognitive Decline for conclusions is an inappropriate standard for public health-

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<sup>2</sup> Luepker et al., 1996.

<sup>3</sup> Ibid.; Seamus P. Whelton, Ashley Chin, Xue Xin, and Jiang He, "Effect of Aerobic Exercise on Blood Pressure: A Meta-Analysis of Randomized, Controlled Trials," *Annals of Internal Medicine* 136, no. 7 (2002): 493-503.

oriented cognitive health research, given the decades-long time frame that would be required of such research, the prohibitive costs, the ethical issues involved, amid what is arguably already a public health crisis.

This study analyzes only six researcher arguments for or against issuing public health recommendations for public health. It is possible that a more complete set of arguments would have emerged with more interviews, although each of the arguments repeated at least once in this sample with the exception of the Logically Derived Policy Argument.

In addition, condensing transcripts into passages inevitably distorts the interview as spoken for the sake of efficiency. The process cuts out important information and reduces the nuances in the dialogue.

#### Implications for public health

I hope that this research project will focus dialogue on policy options in public health gerontology. Researchers pointed to a need to develop consensus around outcomes for cognitive health. They also raised questions about the reliance on RCTs as *the* standard of truth for public health action. The strongest argument made led me to suggest recommending the addition of cognitive health messaging to cardiovascular health programs in public health. Such messaging could both raise awareness about cognitive health in aging and might also provide additional motivation to engage in heart-healthy behaviors that have had low adherence rates to date.

#### Directions for future research

Further research should examine arguments made by cognitive health policymakers, cognitive health industry spokespeople, and members of the public

who have cognitive concerns. In addition, cognitive health provides an opportunity to make even more radical interdisciplinary gestures, such as including adult educators in the conversation. Education and cognition would seem to be a natural fit but have been perhaps been kept divided by the outmoded idea that only children's brains have the capacity to develop and learn. Lastly, future research should approach those involve with policymaking in different countries. The United Kingdom's *Foresight Report on Mental Capital and Wellbeing*,<sup>4</sup> which is designed to promote "mental capital" across the life course, starting at a young age and continuing through life with lifestyle behavior modification, might provide a logical starting point.

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<sup>4</sup> Foresight Mental Capital and Wellbeing Project, *Final Project Report – Executive Summary* (London: The Government Office for Science, 2008).

## Appendix

### Profiles of Cognitive Health Experts Interviewed

**Hugh Hendrie, M.B., Ch.B., D.Sc.:** Geriatric psychiatrist and health services researcher at Indiana University and the Regenstrief Institute, Inc., Bloomington, IN. Chair of the Critical Evaluation Study Committee that conducted the critical literature evaluation for the NIH Cognitive and Emotional Health Project. In 2006 Hendrie served on the Steering Committee of the Healthy Brain Initiative, participating as well in its Surveillance Workgroup. In 2010 he offered the final commentary on the Evidence-Based Practice Center Systematic Review at the State-of-the-Science Conference.

**Jennifer Manly, Ph.D.:** Associate Professor of Neuropsychology, Department of Neurology, the Sergievsky Center and the Taub Institute, Columbia University, New York, NY. She also spoke at the State-of-the-Science Conference. She lists her research interests as 1) cognitive test performance of African American elders, 2) literacy as a proxy for cognitive reserve, and 3) literacy and working memory.

**Leonard Poon, Ph.D.:** An experimental cognitive aging psychologist and Professor Emeritus, Institute of Gerontology, University of Georgia, Athens, GA. His primary research area funded by NIMH and NIA is focused on survival and longevity of the oldest old, the Georgia Centenarian Study. His research includes every-day memory processes in the elderly, cognition and speed of behavior in older adults, clinical memory assessment, cognition in and survivorship of the oldest-old, and changes that occur in cognitive systems with Alzheimer's disease.

**Peter Rabins, M.D., M.P.H.:** The Richman Family Professor for Alzheimer's and Related Disease and Co-Director, Division of Geriatric Psychiatry and Neuropsychiatry, Johns Hopkins School of Medicine, Baltimore, MD, where he has been on faculty since 1978. Member of the Healthy Brain Initiative Prevention Research Workgroup. Co-author of *The 36-Hour Day* (1981, 1991, 1999, 2006), *Practical Dementia Care* (2000), and *Getting Old Without Getting Anxious* (2005).

**George Rebok, Ph.D.:** Professor, Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, and one of the principal investigators of the ACTIVE Trial. Rebok states that his research interests are 1) identification of early risk and protective factors on later life cognitive health and daily function, 2) prevention of age-related cognitive decline, memory loss, depression, and disability, and 3) study of the short- and long-term outcomes of cognitive intervention trials with children and with normal and impaired older adults.

**Yaakov Stern, Ph.D.:** Division Leader of the Cognitive Neuroscience Division of the Sergievsky Center, Professor of Clinical Neuropsychology (in Neurology,

Psychiatry, and Psychology, in the Sergievsky Center and the Taub Institute), Columbia University, New York, NY. He lists his research interests as cognitive reserve, cognitive intervention in normal aging, and the heterogeneity of Alzheimer's disease.

**Peter Whitehouse, M.D., Ph.D.:** Professor of Neurology at Case Western Reserve University, Cleveland, OH, and author of *The Myth of Alzheimer's: What You Aren't Being Told About Today's Most Dreaded Diagnosis*. Whitehouse was the founder of the University Alzheimer Center (now the University Memory and Aging Center) at Case Western Reserve University and University Hospitals Case Medical Center. Whitehouse is also a founder with his wife of The Intergenerational School, an innovative, successful urban public school in Cleveland.



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